THE MINISTRY OF HEALTH OF UKRAINE
ZAPORIZHZHIA STATE MEDICAL AND PHARMACEUTICAL UNIVERSITY

Biological Chemistry Department

BIOLOGICAL CHEMISTRY

SECTION 2: EXCHANGE OF COMPLEX PROTEINS. MOLECULAR BIOLOGY. BIOCHEMISTRY OF INTERCELLULAR COMMUNICATIONS, TISSUES AND PHYSIOLOGICAL FUNCTIONS

HANDBOOK FOR INDEPENDENT WORK
PREPARATION FOR COMPONENT OF USQE 'KROK-1, DENTISTRY'
for students of Speciality "Dentistry"

ZAPORIZHZHIA
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This manual is recommended to use for students of II International faculty (the second year of study) for independent work on Biochemistry discipline at home and in class.

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CONTENT

INTRODUCTION

The concept of development of health care of Ukraine envisages the holding of license integrated exams in higher educational medical institutions for unified quality control of training of specialists in the field of health care. The proposed study guide contains the necessary material for successful preparation for passing the licensing integrated test exam «Krok 1. Dentistry» for students of the Faculty of Medicine, specialty «Dentistry». The notebook covers the entire curriculum of module 2. At the beginning of each topic, students are offered a short theoretical material on the topic, then they get a block of tests to which they must independently find the answer and justify it. This work is published in English.

LESSON №1

1. TOPIC: EXCHANGE OF PURINE AND PYRIMIDINE NUCLEOTIDES. VIOLATION OF NUCLEOTIDE EXCHANGE

1. INFORMATION MATERIAL.

Nucleoproteins are complex proteins, the non-protein component of which are nucleic acids DNA (deoxyribonucleic acid) or RNA (ribonucleic acid). Protein components contain a lot of positively charged amino acids that are arginine and lysine, so they can be classified as polycations (histones). The protein components of histones undergo exchange, just like simple proteins (fig. 1.1).

In the nucleus, histones are tightly bound to DNA (their number is approximately equal by mass), forming a chain of nucleoprotein particles what called nucleosomes, which represent a lower level of DNA packaging in the chromosome. Groups of histones differ in their role in the formation of the nucleosome and the following levels, which caused their division into three subgroups: arginine-rich (H3 and H4), moderately lysine-rich (H2A and H2B) and lysine-rich (H1).

Most non-histone proteins belong to the family of proteins with high electrophoretic mobility that called HMG (High Mobility Group) proteins. According to their structure and functions, these proteins can be divided into three families: HMGN proteins, which directly bind to nucleosomes and facilitate transcription; proteins of the HMGA group, which change the structure of DNA, facilitate interprotein interaction in the preinitiative transcription complex; proteins of the HMGB group are the most common and the most studied, they stabilize nucleosomes and interact with DNA, play an important role in the pathogenesis of malignant tumors.

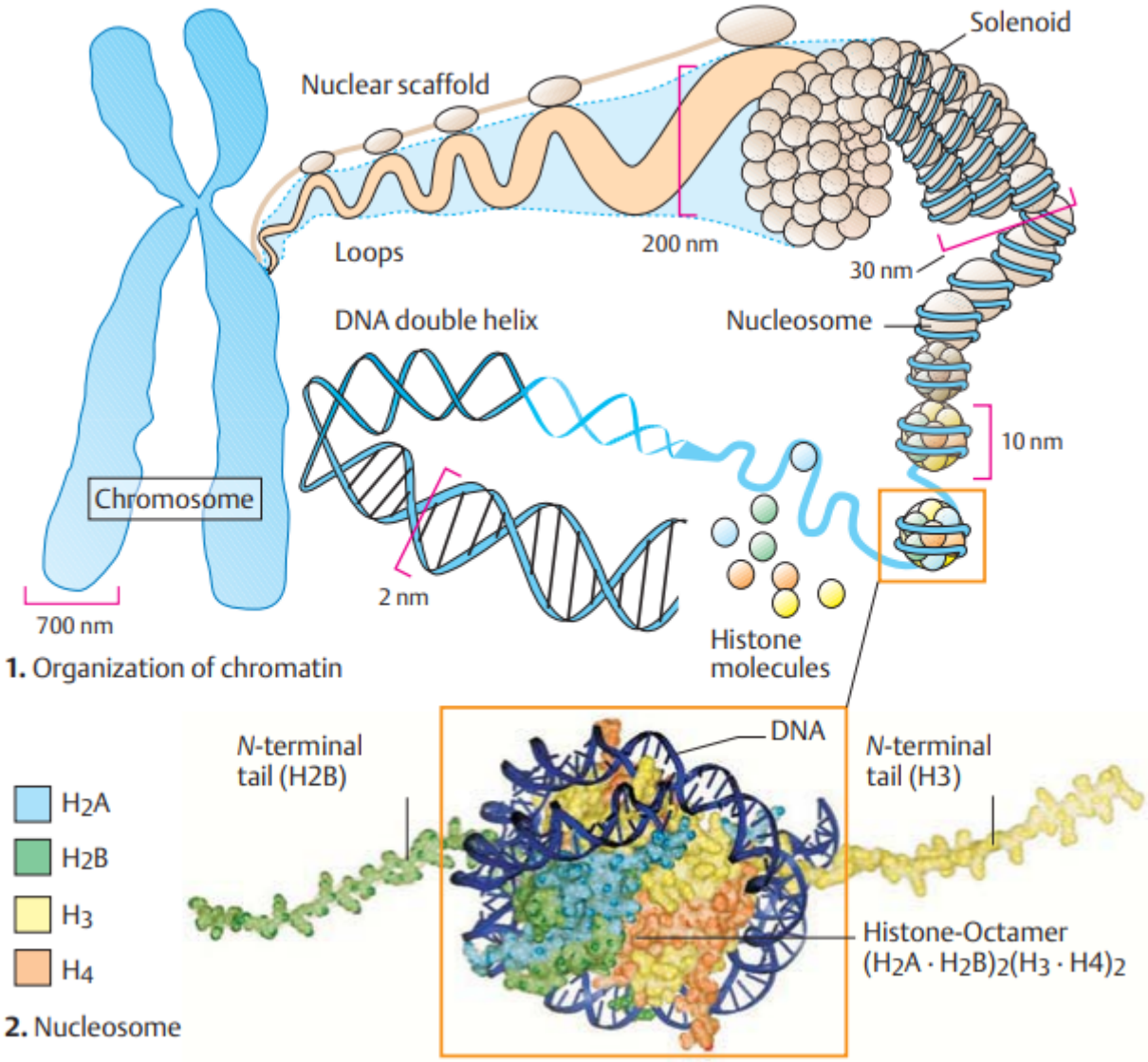


Fig. 1.1. The structure of chromosome

Nucleic acids are linear (rarely cyclic) heteropolymers, the monomers of which are mononucleotides.

In the composition of nucleic acids, mononucleotides are connected by 3',5'-phosphodiester bonds between riboses (deoxyriboses) of neighboring mononucleotides through a phosphoric acid residue (primary structure). One of the ends of the polynucleotide chain ends with a free phosphate (P- or 5'-end), and the other with a non-esterified OH group of C_3-pentose (3'-end). The 5' end is considered initial.

Mononucleotides consist of three components: a nitrogenous base (purine is adenine, guanine or pyrimidine is cytosine, thymine is in the composition of DNA

or uracil ks in the composition of RNA), pentoses (β-D-ribofuranose is in the composition of RNA or β-D-2-deoxyribofuranose is in DNA) and the rest of phosphoric acid (fig. 1.2). Inside the nucleotide, the nitrogenous base and the pentose are connected to each other by an N-glycosidic bond (forming the corresponding nucleoside – adenosine, guanosine, uridine, cytidine, etc.), and phosphoric acid to the pentose by an ester bond. TMP is found only in DNA, and UMP is only in RNA (fig 1.2).

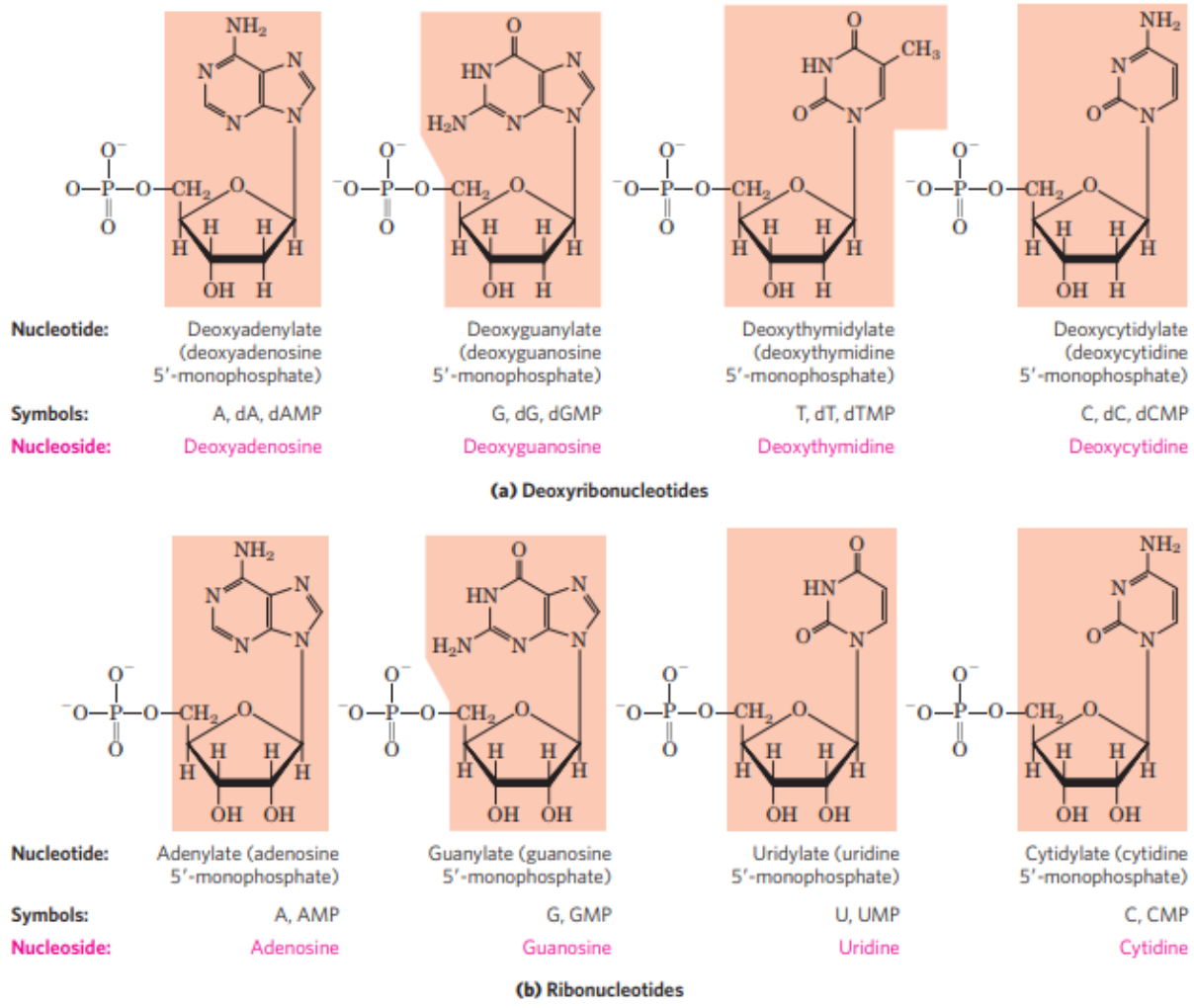


Fig. 1.2. Deoxyribonucleotides and ribonucleotides of nucleic acids.

The name of nucleotides corresponds to the name of the nitrogenous base included in its composition (adenylic/deoxyadenylic acid, guanylic/deoxyguanylic acid, cytidylic/deoxycytidylic acid, thymidylic acid is only in DNA, uridylic acid is only in RNA).

Nitrogen base	Nucleoside	Nucleotide
Adenine	Adenosine	Adenosine monophosphate (AMP) or adenylic acid.
Guanine	Guanosine	Guanosine monophosphate (GMP) or guanylic acid.
Uracil	Uridin	Uridine monophosphate (UMP) or uridylic acid.
Timin	Thymidine	Thymidine monophosphate (TMP) or thymidine acid.
Cytosine	Cytidine	Cytidine monophosphate (CMP)

Nucleotides (in addition to being monomers of nucleic acids) can have an important independent meaning:

- participate in energy (ATP, ADP, AMP), lipid (CTP) and carbohydrate metabolism (UTP);

- perform the role of secondary mediators in hormonal regulation – cyclic nucleotides (cAMP, cGMP);

- perform the role of allosteric regulators of enzyme activity (cAMP);

-are coenzymes (prosthetic groups) of oxidoreductase enzymes – derivatives of nucleotides (NAD+, NADP+, FAD, FMN and their reduced forms).

In addition to the five listed main nitrogenous bases, so-called ***minor purine*** (N6-methyladenine, N2-methylguanine, xanthine, hypoxanthine, 7-methylguanine) and pyrimidine (5-methyl- and 5-oxymethylcytosine, dihydrouracil, pseudouracil, 1-methyluracil, orotic acid, 5-carboxyuracil, 4-thiouracil) bases.

Like many other biopolymers, nucleic acids have structural levels of organization.

DNA

The primary structure of DNA is the order of alternation of deoxyribonucleoside monophosphates (dNMP) in the polynucleotide chain. The bond between the monomers is 3',5'-phosphodiester.

Secondary structure of DNA. In 1953, J. Watson and F. Crick proposed a model of the spatial structure of DNA. According to this model, the DNA molecule has the shape of a helix formed by two polynucleotide chains twisted relative to each other and around a common axis. A double helix twisted to the right, the polynucleotide chains in it are antiparallel, that is, if one of them is oriented in the direction 3'→ 5', then the second - in the direction 5'→ 3'. Therefore, the 5'-end of one chain and the 3'-end of another chain are located at each end of the DNA molecule. Polynucleotide chains are held relative to each other due to hydrogen bonds between complementary purine and pyrimidine nitrogenous bases A and T (two bonds) and between G and C (three bonds).

SYNTHESIS OF MONONUCLEOTIDES

CO_2 and ribose-5-phosphate are necessary for de novo synthesis of mononucleotides. In addition, some replacement amino acids are necessary, so even with complete starvation, the synthesis of nucleic acids is not disturbed. Synthesis occurs with the consumption of ATP.

The role of amino acids in the synthesis of mononucleotides:

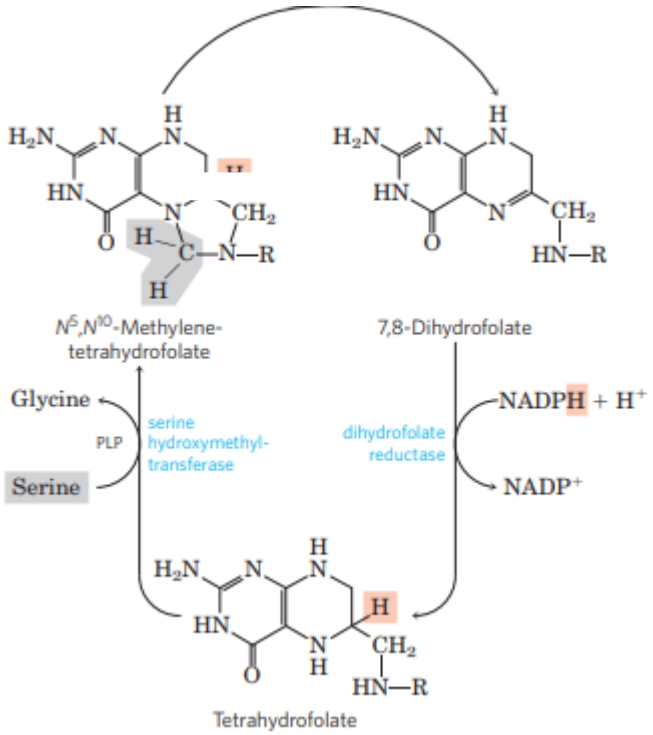
1) Asparagine is an amide group donor.
2) Aspartic acid:
    a) Is a donor of an amino group
    b) Participates in the synthesis of the entire molecule.
3) Glycine:
    a) Is a donor of active C1.
    b) Participates in the synthesis of the entire molecule.
4) Serine is a donor of active C1.

Transfer of one-carbon fragments

There are enzymes in the human body that can remove the C1 group from some amino acids. Such enzymes are complex proteins. As a coenzyme, they contain a derivative of vitamin Bc what is folic acid. There is a lot of folic acid in green leaves, besides, this vitamin is synthesized by intestinal microflora. In the cells of the body, folic acid (FA) is twice reduced (hydrogen is added to it) with the participation of the enzyme NADPH·H2-dependent reductase and is transformed into tetrahydrofolic acid (THFA).

The active fragment C1 is extracted from glycine or serine. In the catalytic center of the enzyme containing THFA, there are two -NH groups that participate in the binding of active C1.

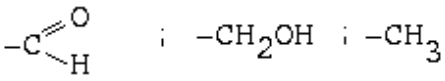
Schematically, the process can be represented as follows:



NADH2, which is formed in the reverse reaction, can be used to reduce pyruvate to lactate (glycolytic oxidoreduction). The reaction is catalyzed by the enzyme glycine synthetase. After that, methylene-THFA is separated from the protein part of the enzyme, and then two variants of its transformations are possible:

1) Methylene-THFA can become a non-protein part of mononucleotide synthesis enzymes.

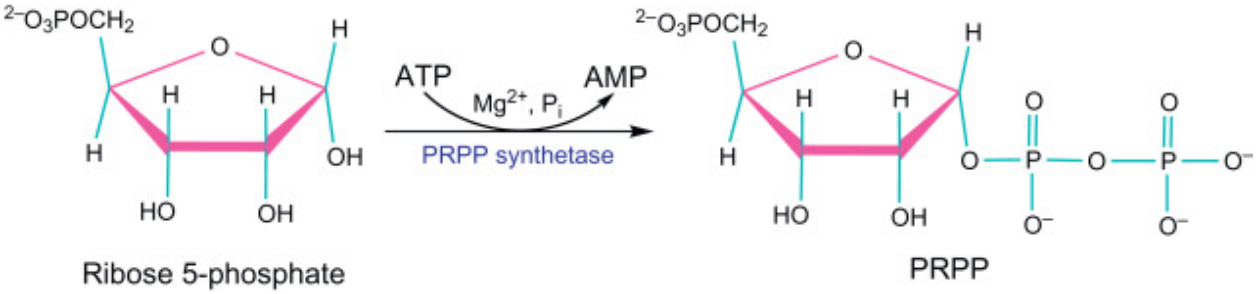
2) The methylene group can change to:



These groups are connected to only one of the nitrogen atoms of THFA, but they can also become substrates for the synthesis of mononucleotides.

Therefore, any of the groups associated with THFA is called active C1

The synthesis of any of the nucleotides requires an active form of ribose phosphate – **phosphoribosyl pyrophosphate (phosphoribosyl diphosphate) (PRPP/ PRDP)**, which is formed in the following reaction:



Phosphoribosylpyrophosphate kinase (PRPP-kinase) is a key enzyme for the synthesis of all mononucleotides. This enzyme is inhibited by the principle of negative feedback by an excess of AMP and GMF. In the case of a genetic defect of PRPP-kinase, there is a loss of sensitivity of the enzyme to the action of its inhibitors. As a result, the production of purine mononucleotides increases, and, therefore, the rate of their decay, which leads to an increase in the concentration of uric acid and the development of gout.

After the formation of PRPP, the reactions of the synthesis of purine and pyrimidine mononucleotides are different.

Differences in the synthesis of purine and pyrimidine mononucleotides:

The peculiarity of the synthesis of **purine** nucleotides is that the cyclic structure of the purine nitrogenous base is gradually completed on the active form of ribose phosphate, as on the matrix. During cyclization, a ready-made purine mononucleotide is obtained.

During the synthesis of **pyrimidine** mononucleotides, a cyclic structure of a pyrimidine nitrogenous base is first formed, which is transferred in its finished form to ribose phosphate.

Synthesis of purine mononucleotides (AMP i GMP)

There are 10 general and 2 specific stages. As a result of joint reactions, a purine mononucleotide is formed, which is the common precursor of future AMP and GMP – inosine monophosphate (IMP), IMP contains hypoxanthine as a nitrogenous base.

The purine ring is built from CO_2, aspartic acid, glutamine, glycine and serine. These substances are either completely included in the purine structure, or give separate groups for its construction (fig. 1.3).

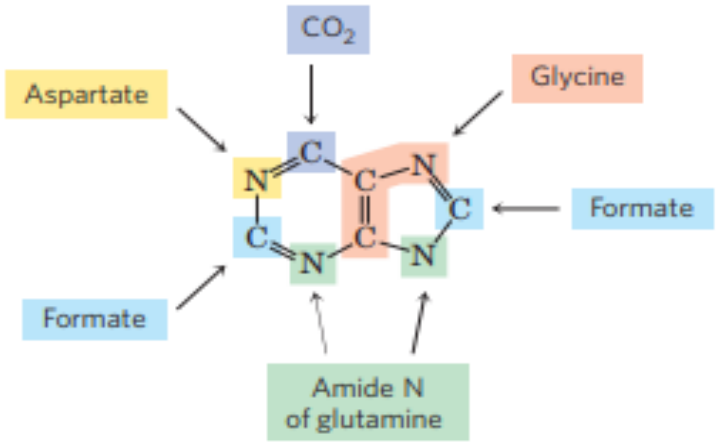


Fig. 1.3. The biosynthetic origins of purine ring atoms.

At the first stage of synthesis, phosphoribosylamine is formed. The enzyme that catalyzes this reaction is called phosphoribosylamidotransferase. It is the key enzyme in the synthesis of all purine mononucleotides. It is regulated according to the principle of negative feedback. Allosteric inhibitors of this enzyme are AMP and GMP. At the second stage, phosphoribosylamine interacts with glycine. The third stage is the inclusion of a carbon atom whose donor is glycine or serine. Then a six-membered fragment of the purine ring is added. The 4th stage is carboxylation using the active form of CO_2 with the participation of vitamin H – biotin. The 5^{th} stage is amination with the participation of an amino group from aspartate. 6^{th} stage is

amination due to the amino group of glutamine. The 7th, final stage is the inclusion of a one-carbon fragment (with the participation of THFA), and a ready-made IMP is formed (fig 1.4).

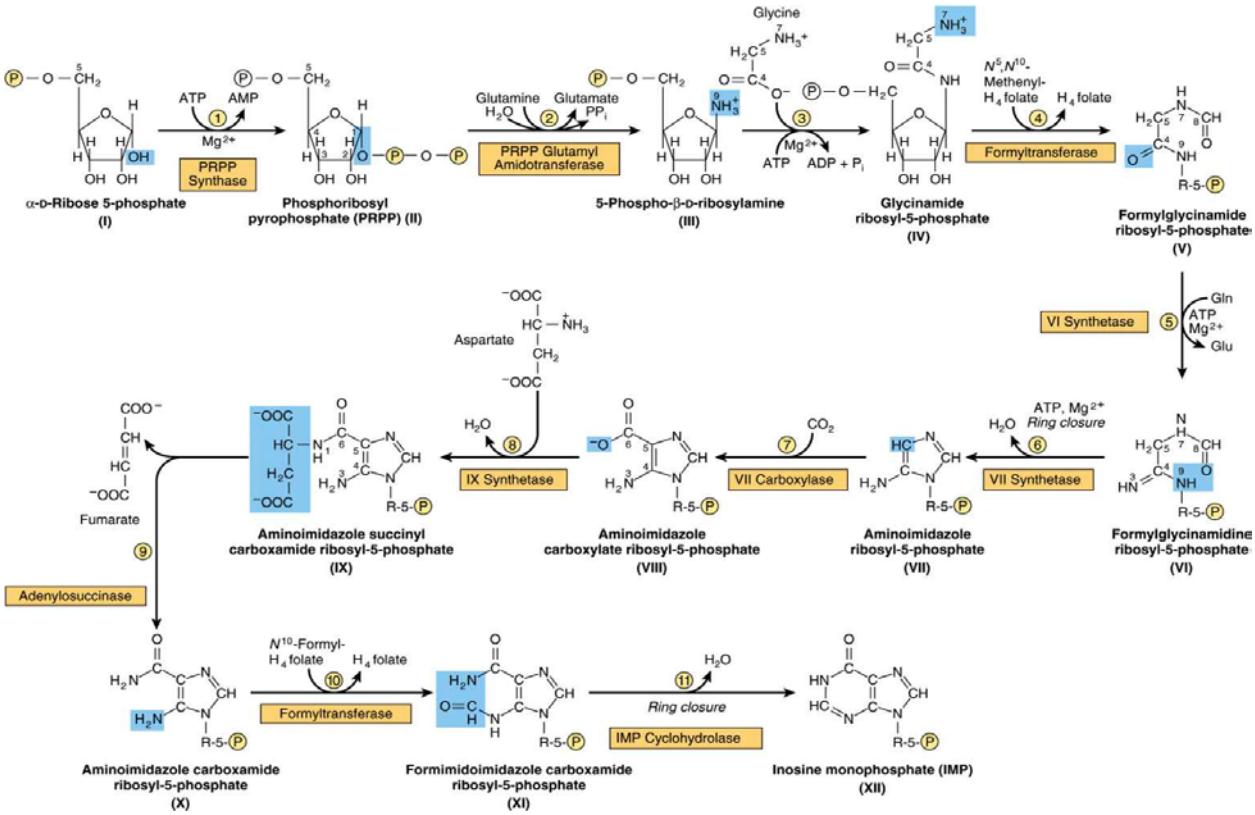


Fig 1.4. IMP biosynthesis

Then youspecific reactions occur, as a result of which IMP is transformed into either AMP or GMP (fig. 1.5).

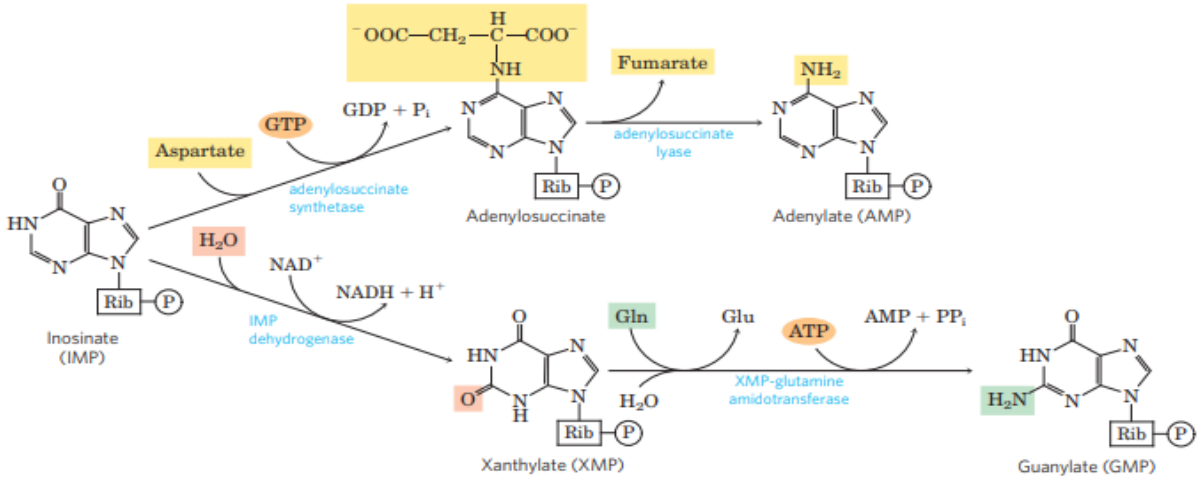


Fig. 1.5. Biosynthesis of AMP and GMP from IMP

With such a transformation, an amino group appears in the molecule, and in the case of transformation into AMP it is in place of the OH group. In the formation of AMP, the source of nitrogen is aspartic acid, and for the formation of GMP, glutamine is necessary.

Next, nucleotides and triphosphates are formed from nucleotide monophosphates (AMP, GMP) with the help of ATP. ATP costs for de novo nucleotide synthesis are very high. This method of synthesis is energetically disadvantageous.

In some tissues, there is an alternative method of synthesis that called recycling purine nitrogenous bases, which were formed during the breakdown of nucleotides (fig. 1.6).

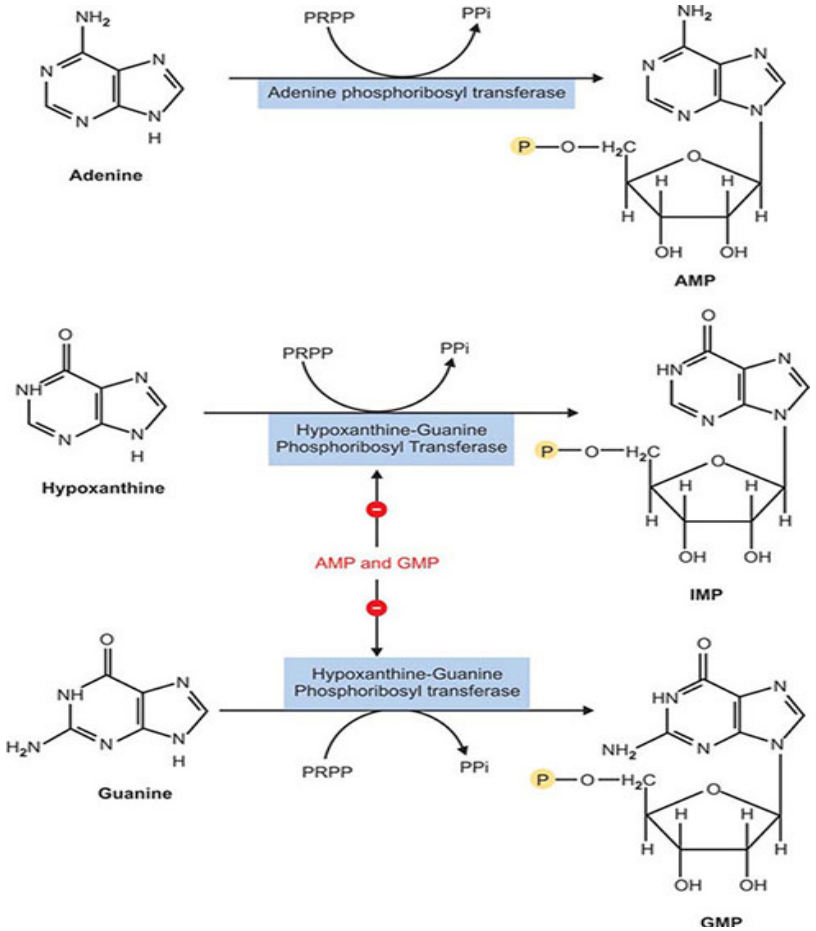


Fig. 1.6. Scheme of recycling purine nitrogenous bases

Enzymes that catalyze reutilization reactions are most active in rapidly dividing cells (embryonic tissues, red bone marrow, cancer cells), as well as in brain

tissues. The diagram shows that the enzyme **guaninehypoxanthinePRPPtransferase** has a wider substrate specificity than **adeninePRPPtransferase**, and in addition to guanine, it can transfer hypoxanthine with the formation of IMG. **Humans have a genetic defect of this enzyme – "Lesch–Nyhan syndrome".**

The disease develops in childhood (in boys), linked to the X-chromosome. Such patients are characterized by hyperuricemia, pronounced morphological changes in the brain and bone marrow, mental and physical retardation, aggression, autoaggression. It is important to note that taking caffeine (purine) in large doses leads to suppression of the process of reutilization of guanine.

Synthesis of pyrimidine mononucleotides

First, the cyclic structure of the pyrimidine nitrogenous base is formed, and only then is the ribose phosphate attached. The first reaction of the synthesis of pyrimidine mononucleotides leads to the formation of carbamoyl phosphate. One of the ATP molecules is a phosphate donor. Orotic acid is the first nitrogenous base on the path of synthesis of pyrimidines (the common precursor of other pyrimidines). Orotic acid is then converted to orotidine monophosphate (OMP). Next, OMP is decarboxylated and UMP is formed (fig. 1.7).

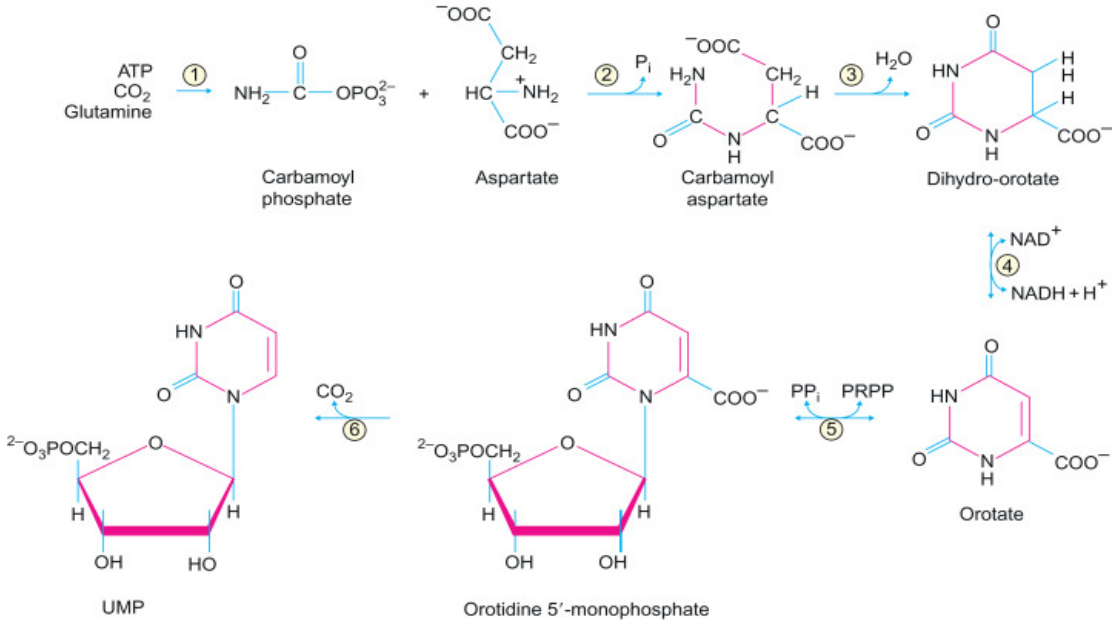


Fig. 1.7. Scheme of de novo synthesis of pyrimidine nucleotides

Other pyrimidine nucleotides can be considered as UMP derivatives. For CTP, the source of the NH_2 group is the amide group of glutamine (fig. 1.8).

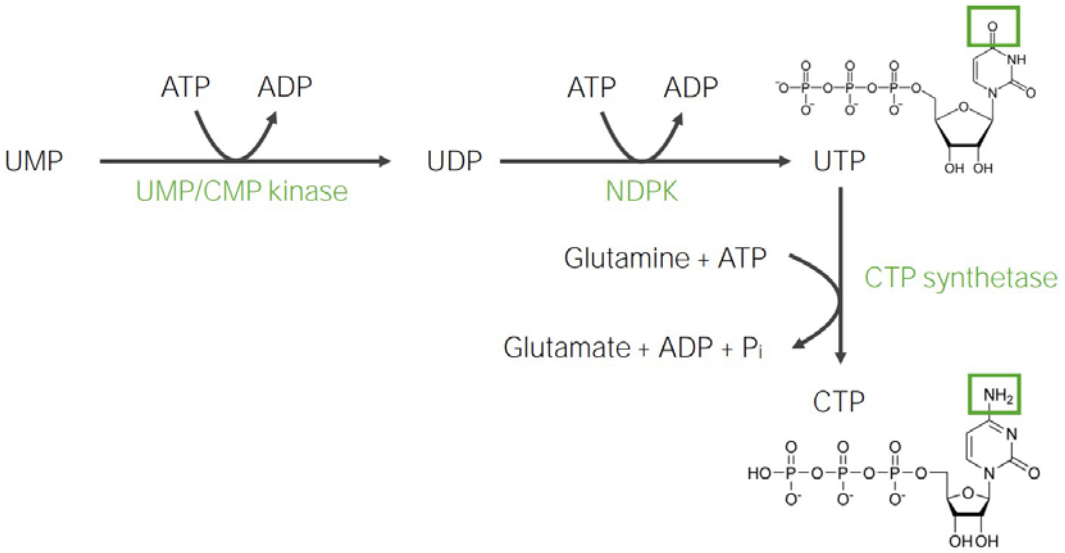


Fig. 1.8. Scheme of CTP

Enzymes of exchange of pyrimidine nucleotides are able to recognize in the substrate not only the nitrogenous base, but also the amount of phosphoric acid residues. As shown in the diagram, cytidine nucleotides are formed only on the basis of the triphosphate form.

A rare hereditary disease is described that called orotaciduria, in which the transformation of orotate into UMP is disturbed. Up to 1.5 g of orotate is excreted in the urine (1000 times more than the norm) and pyrimidine nucleotide deficiency develops. Uridine or cytidine is used to treat orotaciduria.

Substrates for RNA synthesis are ATP, GTP, CTP, UTP – ribonucleotides, and for DNA synthesis – nucleotides containing deoxyribose – dNTP (deoxyribonucleotides). Deoxyribose is a derivative of ribose, where the hydroxyl group at the second carbon atom is replaced by hydrogen with the loss of an oxygen atom. Deoxyribonucleotides are formed from ribonucleotides in the form of nucleoside diphosphates (NDF (mostly)) and nucleoside triphosphates (NTP) under the action of the enzyme NDP reductase.

The source of hydrogen in this reaction is the enzyme NDP-reductase, which contains two SH groups. The regeneration of the reduced form of NDP-reductase

occurs with the help of a chain of reactions, where the direct donor of hydrogen is a special protein that is thioredoxin, which receives two hydrogen atoms from the glutathione tripeptide (G-SH), which at the same time turns into an oxidized form. Oxidized glutathione is further reduced by the enzyme glutathione reductase, which uses NADP·H2 for this (fig. 1.9).

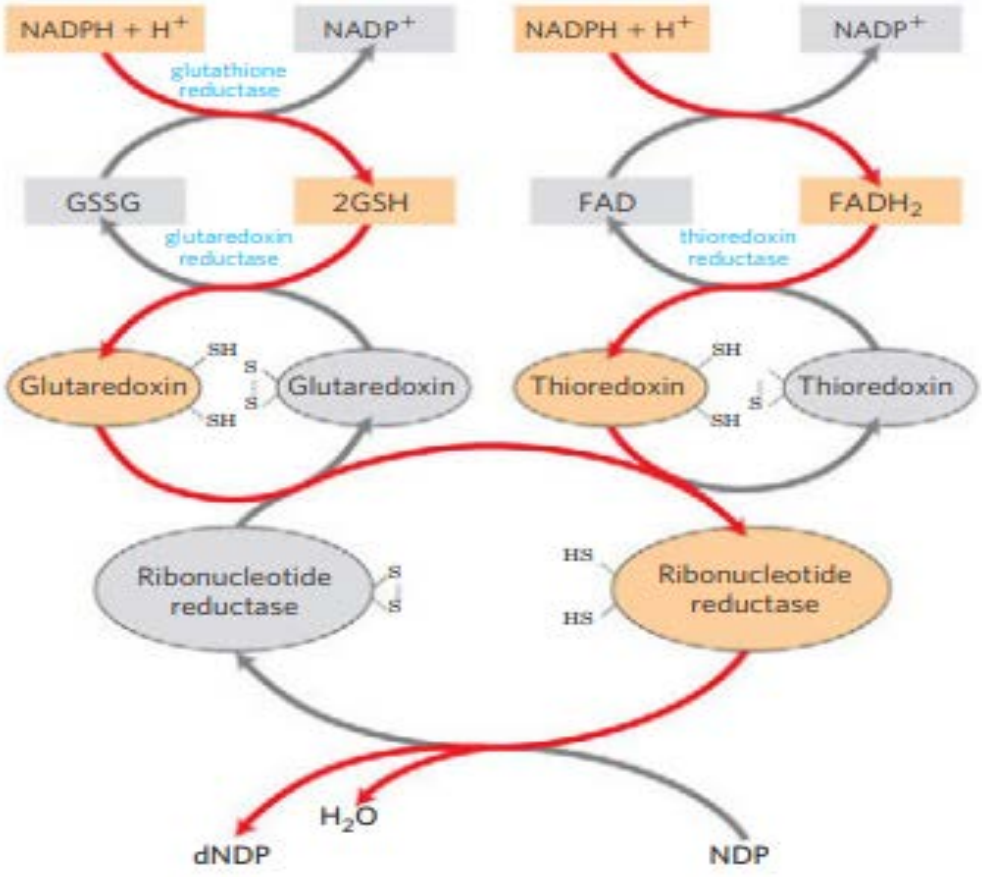


Fig. 1.9. Scheme of reduction of ribonucleotides to deoxyribonucleotides by ribonucleotide reductase

All dNDP, including dUDP, are formed in this way, but they are not included in the composition of DNA, but are transformed into thymidyl nucleotides. For this is needed dUMP (fig. 1.10). TMP can be formed both in deoxyform (dTMP) and in oxy-TMP. The reaction of formation of (d) TMP is catalyzed by an enzymethymidylate synthetase, its coenzyme includes THFA. This enzyme is a target for many pharmacological drugs. Permanent thymidyl nucleotides are necessary only for DNA synthesis, therefore inhibition of this enzyme inhibits cell

division, but does not affect the rate of synthesis of messenger RNA (i-RNA) and proteins. Thymidylate synthetase inhibitors are used in cancer therapy.

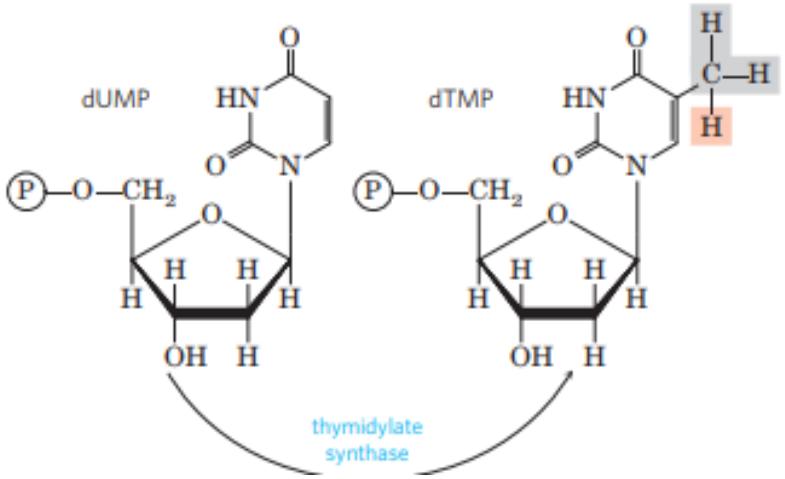


Fig. 1.10. Scheme of synthesis dTMP

There are 2 main groups of such substances:

1) Competitive inhibitors are substances similar to the substrate. For example, its derivative is dUMP-5-fluorouracil.

2) Substances similar to thymidylate synthase coenzyme – THFA. For example, the antivitamin FK is the drug methotrexate.

The formed (d) TMP undergoes phosphorylation to (d) TTP:

(d) TMP⇒(d) TDP⇒(d) TTP.

The remaining mononucleotides can be used for DNA synthesis only in triphosphate deoxyform: dATP, dGTP, dCTP.

Catabolism of pyrimidine nitrogenous bases

Pyrimidine nitrogenous bases undergo destruction to CO_2, NH_3 and β-alanine (cytosine, uracil) or β- aminoisobutyrate (thymine). Purinesnitrogenous bases preserve the cyclic structure of the purine. End product: uric acid is a substance of purine nature. The amino group of pyrimidine nitrogenous bases can be hydrolytically cleaved very easily, when the nitrogenous base is still in the composition of nucleoside, mononucleotide and even in the composition of nucleic

acid. But since uracil is not part of DNA in the body, deamination of cytosine and its transformation into uracil is perceived by the cell as an error and is corrected.

β-alanine is usually degraded to CO_2, H_2O and NH_3, but can sometimes be used for the synthesis of carnosine and anserine peptides in muscle tissue. In microorganisms β-alanine is also used for the synthesis of HS-CoA. Urea, which is formed from ammonia, can also be considered the final product of the decomposition of pyrimidine nitrogenous bases (fig. 1.11).

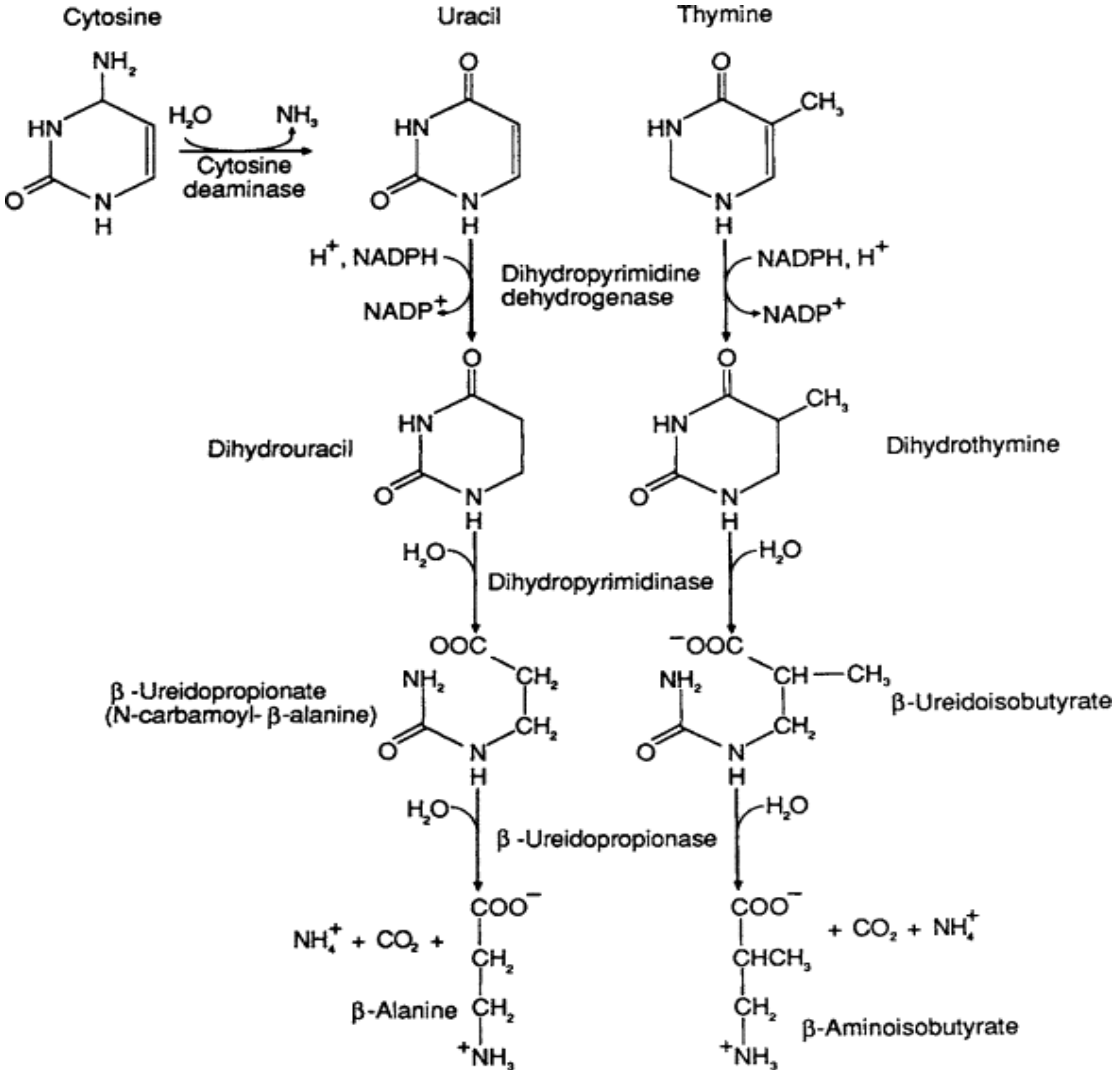


Fig. 1.11. Scheme of pathways for pyrimidine nitrogenous bases catabolism

Thymine decomposes like uracil, but the CH_3 group is preserved instead β-alanine is formed β- aminoisobutyrate (α-methyl-β-alanine, fig. 1.11). Since thymine is found only in DNA, then according to the level β-aminoisobutyrate in urine is used to judge the intensity of DNA decay.

Catabolism of purine nitrogen bases

The decay begins with the cleavage of the amino group (its cleavage is also possible in DNA). The enzyme **adenosine deaminase** is sometimes formed in a defective mutant form, which leads to congenital immunodeficiency, since nucleotides are regulators of leukocyte functions. In AIDS, the activity of this enzyme is also significantly reduced.

The formed inosine undergoes phosphorolysis. Next, hypoxanthine is oxidized twice by removing hydrogen with the simultaneous addition of water and the formation of uric acid (fig. 1.12).

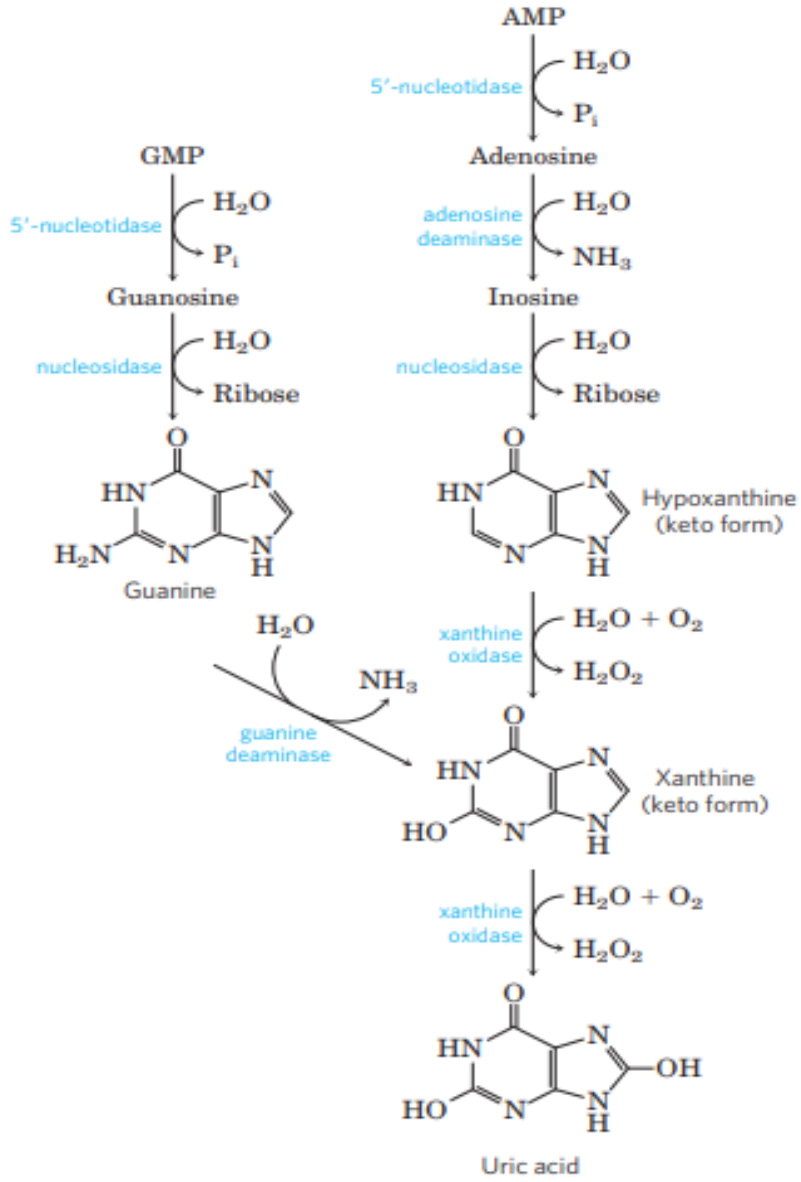


Fig. 1.12. Scheme of catabolism of purine nucleotides

These two identical reactions are catalyzed by the same enzyme that is **xanthine oxidase**. Xanthine oxidase can exist in two forms:

- D-form is dehydrogenase.
- O-form is oxidase.

The forms differ from each other in the ability to transfer 2 hydrogen atoms. The D-form transfers hydrogen to the main respiratory chain of mitochondrial oxidation, and the O-form immediately transfers to oxygen with the formation of H_2O_2. The D-form can change to the O-form by limited proteolysis with the cleavage of a small part of the molecule.

A genetic defect of xanthine oxidase is manifested by xanthineuria and the formation of xanthine stones in tissues. In this case, the source of xanthine is guanine, which is subject to hydrolytic deamination.

In humans, uric acid is the end product of purine catabolism.

Uric acid is one of the normal components of urine. About 1 gram of uric acid is produced in the body per day, but its intensive reabsorption occurs in the kidneys of the human body. The concentration of uric acid in the blood is maintained at a constant level of 0.12-0.30 mmol/l.

Functions of uric acid:

1. It is a powerful stimulant of the central nervous system, suppressing phosphodiesterase, which acts as a mediator of the action of the hormones adrenaline and noradrenaline. Uric acid prolongs (extends) the effect of these hormones on the central nervous system.

2. Possesses antioxidant properties – able to interact with free radicals.

The level of uric acid in the body is controlled at the genetic level. People with a high level of uric acid are characterized by increased vitality.

However, the increased content of uric acid in the blood (hyperuricemia) is dangerous. Uric acid itself and, especially, its urate salts (sodium salts of uric acid) are poorly soluble in water. Even with a slight increase in concentration, they begin to precipitate and crystallize, forming stones. Crystals are perceived by the body as

a foreign object. In the joints, they are phagocytosed by macrophages, the cells themselves are destroyed, and hydrolytic enzymes are released from them. This leads to an inflammatory reaction, accompanied by severe pain in the joints. This disease is called **gout**. Another disease in which urate crystals are deposited in the bladder is known as **urolithiasis**.

For the treatment of gout and urolithiasis, the following are used:

– xanthine oxidase enzyme inhibitors. For example, allopurinol is a substance of purine nature, is a competitive enzyme inhibitor. The action of this drug leads to an increase in the concentration of hypoxanthine. Hypoxanthine and its salts are more soluble in water and are more easily removed from the body;

– diet, excluding foods rich in nucleic acids, purines and their analogues: fish roe, liver, meat, coffee and tea;

– Lithium salts because they are more soluble in water than sodium urates.

2. TASKS FOR INDEPENDENT WORK.

In the table with test tasks, underline the key words, choose the correct answer and justify it:

1	The doctor prescribed allopurinol to a patient with gout. What pharmacological property of allopurinol provides a therapeutic effect in this case? A. Slowing down of reutilization of pyrimidine nucleotides B. Acceleration of nucleic acid synthesis C. Competitive inhibition of xanthine oxidase	

	D. Acceleration of catabolism of pyrimidine nucleotides E. Increasing the rate of excretion of nitrogen-containing substances	
2	A 65-year-old man suffering from gout complains of pain in the kidney area. An ultrasound examination revealed the presence of kidney stones. As a result of which process are kidney stones formed? A. Heme decay B. Protein catabolism C. Restoration of cysteine D. Ornithine cycle E. Decay of purine nucleotides	
3	A 42-year-old man suffering from gout has an increased concentration of uric acid in his blood. He was prescribed allopurinol to reduce the level of uric acid. Allopurinol is a competitive inhibitor of which enzyme? A. Hypoxanthine phosphoribosyltransferases B. Guanindeaminases C. Adenine phosphoribosyl transferases D. Adenosine deaminase	

	E. Xanthine oxidase	
4	The patient has an increased content of uric acid in the blood, which is clinically manifested by a pain syndrome due to the deposition of urates in the joints. As a result of which process is this acid formed? A. Decay of pyrimidine nucleotides B. Heme catabolism C. Cleavage of proteins D. Decay of purine nucleotides E. Reutilization of purine bases	
5	With hereditary orotaciduria, the excretion of orotic acid is many times higher than the norm. The synthesis of which substances will be disturbed in this pathology? A. Biogenic amines B. Purine nucleotides C. Urea D. Pyrimidine nucleotides E. Uric acid	
6	Allopurinol that is a competitive inhibitor of xanthine oxidase, was prescribed to a patient with urolithiasis after examination. The basis for this was the chemical analysis of kidney stones, which consisted mainly of:	

	A. Calcium sulfate B. Sodium urate C. Calcium oxalate monohydrate D. Calcium phosphate E. Calcium oxalate dihydrate	
7	The oncology patient was prescribed the drug methotrexate, to which the target cells of the tumor later became desensitized. The gene expression of which enzyme changes? A. Dihydrofolate reductases B. Folate oxidases C. Thyminases D. Deaminases E. Folate decarboxylase	
8	A 46-year-old patient turned to the doctor with a complaint of pain in the joints, which worsens on the eve of a change in weather. An increased concentration of uric acid was found in the blood. Increased decay of which substance is the most likely cause of the disease? A. TMP B. AMP C. CMP D. UMP E. UTP	

9	A 65-year-old man suffering from gout complains of pain in the kidney area. An ultrasound examination revealed the presence of kidney stones. An increase in the concentration of which substance is the most likely cause of stone formation in this case? A. Uric acid B. Cholesterol C. Urea D. Bilirubin E. Cystine	
10	Pterin derivatives (aminopterin and methotrexate) are inhibitors of hydrofolate reductase, as a result of which they suppress the regeneration of tetrahydrofolic acid from dihydrofolate. These drugs lead to inhibition of the intermolecular transport of one-carbon groups. The biosynthesis of which polymer is inhibited at the same time? A. Glycosaminoglycans B. DNA C. Homopolysaccharides D. Squirrel E. Gangliosides	

11	On the basis of laboratory analysis, the diagnosis of gout was confirmed in the patient. To make a diagnosis, the content was determined: A. Creatinine in urine B. Uric acid in blood and urine C. Residual nitrogen in the blood D. Urea in blood and urine E. Ammonia in urine	
12	In the synthesis of purine nucleotides, some amino acids, vitamin derivatives, phosphoric esters of ribose are involved. The coenzyme form of which vitamin is a carrier of one-carbon fragments in the synthesis of purine nucleotides? A. Folic acid B. Pantothenic acid C. Nicotinic acid D. Riboflavin E. Pyridoxine	
13	A 50-year-old patient was diagnosed with gout, and hyperuricemia was detected in the blood. The metabolism of which substances is disturbed: A. Amino acids B. Carbohydrates C. Lipids	

	D. Pyrimidines E. Purines	
14	On the basis of laboratory analysis, the diagnosis of gout was confirmed in the patient. What analysis was carried out: A. Determination of ammonia in urine. B. Determination of residual nitrogen in the blood. C. Determination of creatinine in urine. D. Determination of urea in blood and urine. E. Determination of uric acid in blood and urine	
15	What metabolite should be used to normalize the metabolism of a newborn child who is gaining weight poorly, an increased content of orotic acid was detected in the urine, which indicates a violation of the synthesis of pyrimidine nucleotides? A. Adenosine. B. Histidine. C. Guanosine. D. Thymidine. E.Uridin.	

16	An 8-year-old boy has Lesch-Nyhan disease. The concentration of uric acid in the blood is increased. Specify the violation of which process is the cause of this hereditary disease? A. Decay of pyrimidine nucleotides. B. Decay of purine nucleotides. C. Synthesis of pyrimidine nucleotides. D. Synthesis of purine nucleotides. E. Reutilization of purine bases.	

3. <u>LITERATURE. See page 320.</u>

LESSON №2

2. TOPIC: BIOSYNTHESIS OF NUCLEIC ACIDS. PROTEIN BIOSYNTHESIS AND ITS REGULATION

1. INFORMATION MATERIAL

DNA replication

Replication (copying, "independent reproduction" of DNA) is a complementary synthesis of DNA on a DNA matrix. eplication occurs only during cell division, it is based on a semi-conservative mechanism. The DNA molecule unravels and its single chains are formed by exact copies of the original DNA, that is, the synthesized DNA is similar to itself and the mother DNA (fig. 2.1).

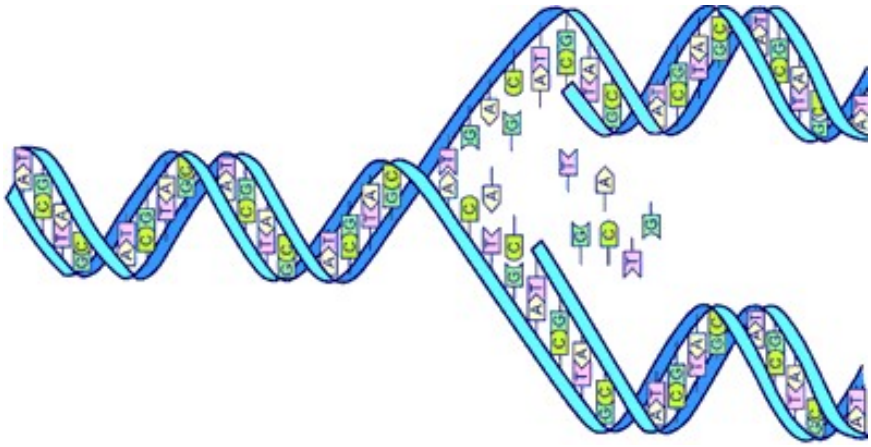


Fig. 2.1. Scheme of DNA synthesis

DNA replication requires the presence of:

1. of four deoxyribonucleosides-5′- triphosphates;
2. matrices in the form of double-stranded DNA;
3. seeds (primer);
4. enzymes and regulatory factors;
5. metal ions (Mg^{2+}, Mn^{2+}).

A number of proteins and enzymes are involved in the reproduction of the replication fork. Thus, DNA topoisomerases (I, II and III), possessing nuclease activity, take part in the regulation of DNA supercoiling. For example, DNA

topoisomerase I breaks the phosphoester bond in one of the chains of the double helix and covalently attaches to the 5’-end at the point of the break. At the end of the formation of the replicative fork, the enzyme eliminates the break in the chain and separates from the DNA (fig. 2.2).

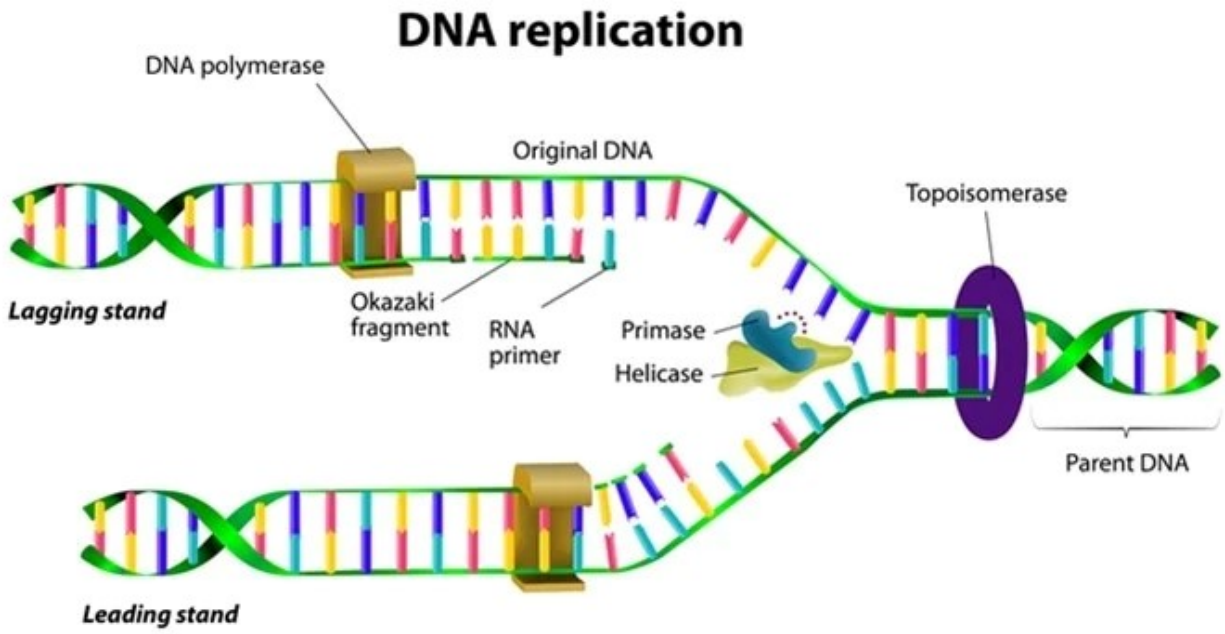


Fig. 2.2. Diagram of the replication process

The rupture of hydrogen bonds in a double-stranded DNA molecule reproduces **DNA helicase** (fig. 2.2)**.** The enzyme DNA helicase uses the energy of ATP to unwind the DNA double helix.

As a result, the section of the supercoiled DNA molecule is untwisted. **SSB proteins** (single strand binding proteins, i.e., proteins that bind to single-stranded DNA strands) take part in maintaining this section of DNA in an unwound state. SSB-proteins, without covering nitrogenous bases, bind to single-stranded DNA along the entire length of the separated chains and thus prevent their complementary twisting and the formation of “hairpins”.

The increase of the DNA chain (elongation) occurs in the direction from the 5’ to the 3’ end. The enzyme that catalyzes this reaction is **DNA-dependent DNA polymerase** (fig. 2.2)**.**

Replication in prokaryotes begins with a small area – the origin, wherea process is initiated, the main point of which is the separation of DNA chains. Later, during replication, such a replication bubble grows in opposite directions. On each side of the vesicle there is a so-called “replication fork”, at the base of which DNA synthesis takes place. The unit of replication in eukaryotes is called a replicon. In contrast to eukaryotes, in prokaryotes both DNA chains are synthesized as a dimer DNA polymerases III. It is important to note that in prokaryotes, until the next moment, three DNA polymerases are known – Pol I ,Pol II and Pol III , the first of which is mainly responsible for DNA repair, the third for DNA replication, and the function of the second is to replace Pol III in extreme cases, such as, for example, mutagenic DNA repair.

DNA replication in eukaryotesconsists of three stages: initiations, elongations and terminations.

In the cells of eukaryotes there are various untangling enzymes and regulatory factors, DNA polymerases, DNA ligases (take part in the cross-linking of Okazaki fragments and repair processes).

DNA methylation. After DNA replication, its methylation occurs – an important covalent modification necessary for the regulation of gene activity. The substrate of DNA methylation is cytosine (a metal group attaches to the fifth atom of the ring to form 5-methylcytosine).

Repair of damaged DNA. Under the influence of chemical, physical and other factors of the external environment, DNA molecules can be damaged, which is mainly associated with disruption of replication processes, DNA molecule breakage, loss of nitrogenous bases or violation of complementarity. Thus, during depurination, deoxyribose residues that do not have a nitrogenous base appear in DNA. During deamination under the influence of nitric acid and nitrites, cytosine is converted into uracil, adenine into hypoxanthine, and guanine into xanthine. Under the influence of ultraviolet light, thymine dimers are formed (fig. 2.3), which interfere with the normal progress of DNA polymerase and the stopping of DNA synthesis between 2 adjacent thymine residues in one DNA chain. In the process of

evolution, certain mechanisms of reparation (restoration) of damaged DNA were formed in the cells of living organisms.

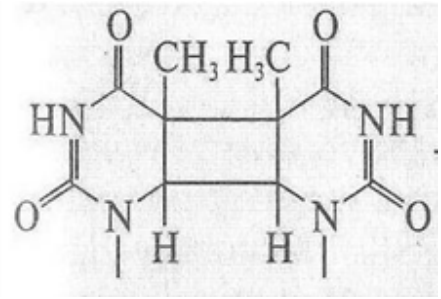


Fig. 2.3. Structure of thymine dimers

1. Repair of damage caused by the action of ultraviolet proceeds sequentially with the participation of the enzyme system: UV-specific endonuclease, DNA polymerase, DNA ligase. Violation of such repair leads to a hereditary disease – xeroderma pigmentosum, in which the synthesis of UV-specific endonuclease is genetically impaired.

2. Repair of deamination of cytosine to uracil involves the participation of enzymes: uracil-DNA-glycosidase, endonuclease, DNA-polymerase, DNA-ligase.

Thus, the biological role of DNA repair consists in the elimination of damage in DNA molecules, preventing the formation of hereditarily fixed violations of the genetic material – mutations. One of the reasons for the occurrence of a number of hereditary diseases and cancers is precisely the violation of DNA repair. Each of the damages is quickly eliminated, if the cell in which it occurred is not destined to die.

Transcription

Transcription(transcription) is the transfer of genetic information between different classes of nucleic acids. In contrast to replication, not the entire DNA molecule is copied, but only its individual fragments (cistrons). During transcription, various types of RNA (mRNA, tRNA, rRNA) are formed, which participate in protein biosynthesis. DNA cistrons contain information about the structure of all types of RNA and the structure of all body proteins.

A distinction is made between forward (from DNA to RNA) and reverse (from RNA to DNA) transcription. Reverse transcription was first discovered in RNA-containing viruses, which is provided by a special enzyme – *reverse transcriptase, or revertase.*

The process of transcription by the enzyme DNA-dependent RNA polymerase. Prokaryotes have one RNA polymerase, which consists of 5 different protein subunits. Eukaryotes have three RNA polymerases (I, II and III). These are proteins that differ from each other in the specificity of transcription. RNA polymerase I is responsible for rRNA gene transcription, RNA polymerase II for mRNA synthesis, and RNA polymerase III for tRNA and 5S rRNA synthesis. These enzymes catalyze the extension of the polynucleotide chain only in the 5′ direction→3′.

During transcription, all types of RNA are formed (mRNA, rRNA and tRNA). All pre-RNAs are linear chains that do not form a ring. They are much longer than cytoplasmic RNAs, so they undergo post-transcriptional processing (maturation) in the nucleus, after which they acquire their functional activity.

Medicines are often inhibitors of nucleic acid synthesis.

Stages of protein synthesis

The molecular mechanisms of ribosomal translation in prokaryotes and eukaryotes have similar features and are divided, as in the synthesis of other biopolymers, into initiation, elongation and termination stages.

1. Initiation of broadcast.

A prerequisite for the start of the functioning of the ribosomal protein synthesizing system is the formation of an initiating complex, which includes:

- 40s and 60s subunits connected to each other in the 80s ribosome; a complete ribosome has two structural sites for binding tRNA molecules loaded with aminoacyl residues during translation: an aminoacyl (A-) site and a peptidyl (P-) site, the first of which is connected to aminoacyl-tRNA during translation, and the second with peptidyl-tRNA.

- mRNA that necessarily has a 7-methylguanyl “cap” at the 5’-end.

- met-tRNAi – a special type of tRNA that accepts and delivers the first, initiating amino acid – methionine – to the ribosome.

Thus, methionine becomes the N-terminal amino acid for most eukaryotic proteins. In prokaryotes, the first, initiating, amino acid is modified methionine-*formylmethionine*.

- protein initiation factors; in particular, the formation of a complete 80s ribosome from subunits and its stabilization require the presence of initiation factors eIF-3, eIF-4C and eIF-6.

- GTP and ATP coenzymes, which provide energy for various stages of initiation.

2. Elongation of the polypeptide chain.

Pure elongation consists in the formation of peptide bonds between amino acid residues.

The prerequisite for the beginning of elongation is binding to the A-site of the ribosome of the 2nd amino acid connected to tRNA. This amino acid corresponds to the mRNA codon that follows the initiation (i.e., AUG) codon.

The formation of a peptide bond between the first and second amino acids is catalyzed by the enzyme peptidyltransferase.

In the course of the peptidyl transferase reaction, the peptide fragment is transferred to an amino acid in such a way that as a result of the reaction, the new peptide formed becomes bound to the A-site of the ribosome. tRNA, which was initially bound to the P-site, is released.

Translocation reaction

After the formation of a peptide bond, the elongated peptide connected to tRNA moves from the A-site to the P-site – the process of translocation. Elongation protein factor eEF-2 is involved in translocation. The energy needs of translocation are provided by the GTPase reaction of splitting GTP to GDP.

6. Termination of broadcast.

Termination occurs when the translating ribosome reaches one of the terminating codons – UAA, UGA or UAG. The occurrence of a terminating codon in the A-site is recognized by protein releasing factors, which cause hydrolysis of the bond between the peptide and the tRNA molecule occupying the P-site of the ribosome.

Post-translational modification of peptide chains

Some proteins require additional post-translational modification. These modifications can greatly expand the variety of possible proteins, giving them new capabilities. Examples of post-translational modifications are the addition of various functional groups, the addition of lipids and carbohydrates, the change of standard amino acids to non-standard ones (for example, the formation of citrulline), structural changes (for example, the formation of disulfide bridges between cysteines), removal of a part of the protein as at the beginning (signal sequence, start-codon), and in some cases in the middle.

2. TASKS FOR INDEPENDENT WORK.

In the table with test tasks, underline the key words, choose the correct answer and justify it:

1	From nitrates, nitrites and nitrosamines, nitrous acid is formed in the body, which causes the oxidative deamination of nitrogenous bases of nucleotides. This can lead to a point mutation - replacing cytosine with: A. Adenin B. Uracil C. Guanin	

	D. Inosine E. Timin	
2	In the experiment, it was shown that when irradiated with ultraviolet light, skin cells of patients with xeroderma pigmentosum, due to a defect of the repair enzyme, restore the native structure of DNA more slowly than the cells of healthy people. What enzyme does this process use? A. RNA ligases B. Endonucleases C. DNA gyrases D. DNA polymerases E. Primase	
3	RNA containing the human immunodeficiency virus penetrated inside the leukocyte and, with the help of the enzyme revertase, forced the cell to synthesize viral DNA. The basis of this process is: A. Covariant replication B. Operon depression C. Reverse transcription D. Reverse Broadcast E. Operon repression	
4	It has been established that some compounds, for example, fungal	

	toxins and some antibiotics, can inhibit the activity of RNA polymerase. Violation of which process occurs in the cell in case of inhibition of this enzyme? A. Transcriptions B. Broadcasts C. Processing D. Replications E. Reparations	
5	It was proved that the molecule of immature i-RNA (pro-i-RNA) contains more triplets than the amino acids found in the synthesized protein. This is explained by the fact that the broadcast is normally preceded by: A. Mutation B. Replication C. Initiation D. Processing E. Reparation	
6	HIV T-lymphocyte virus damage was detected. At the same time, the enzyme of the virus, reverse transcriptase (RNA-dependent DNA polymerase) catalyzes the synthesis: A. DNA on a viral RNA template	

	B. i-RNA on a viral protein matrix C. Viral DNA on a DNA template D. Viral i-RNA on a DNA matrix E. DNA on viral r-RNA	
7	An employee of a chemical enterprise was exposed to nitrous acid and nitrites, which cause the deamination of cytosine in the DNA molecule, as a result of violating the rules of safe work. What enzyme initiates a chain of repair processes? A. Uridine DNA glycosidase B. Orotidyl monophosphate decarboxylase C. DNA-dependent RNA polymerase D. Thymidylate synthase E. Cytidine triphosphate synthetase	
8	The synthesis of i-RNA takes place on the DNA matrix, taking into account the principle of complementarity. If the triplets in DNA are as follows - ATG-CGT, then the corresponding codons of i-RNA will be: A. UAC-GCA B. ATG-CGT C. TAG-UGU D. AUG-CSU	

	E. UAG-CSU	

3. **LITERATURE. See page 320.**

LESSON №3

3. TOPIC: CHROMOPROTEINS. HEMOGLOBIN METABOLISM AND ITS DISORDERS. METABOLISM OF PORPHYRINS

1. INFORMATION MATERIAL.

Chromoproteins are complex proteins, the prosthetic group of which has a specific staining. These include hemoproteins, flavoproteins and metalloproteins.

Hemoproteins include hemoglobin and its derivatives, myoglobin, chlorophyll-containing proteins and some enzymes (cytochromes, catalase, peroxidase). All of them have as a non-protein component structurally similar metal porphyrins (iron porphyrins are in heme, cytochromes, catalase; magnesium porphyrins are in chlorophyll) and a protein part that is different in composition and structure.

Hemoglobin as a protein component contains globin, and non-protein – heme – a pigment that gives blood its characteristic red color. Species differences in hemoglobin are due to globin, while heme is the same in all types of hemoglobin (fig. 3.1).

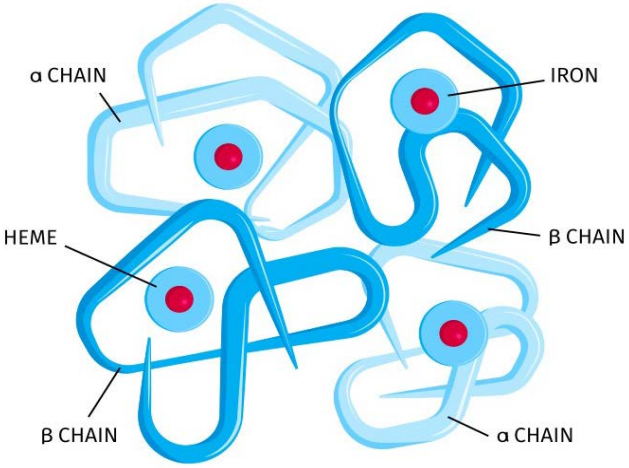


Fig. 3.1. Molecular structure of hemoglobin

The unique role’of hemoglobin is to transport oxygen from the lungs to the tissues and carbon dioxide from the tissues to the lungs. Also, hemoglobin accounts for most of the buffer capacity of plasma, which is due to its significant

concentration in the blood and the relatively high content of histidine in its polypeptide chains. The acidity of hemoglobin depends on its form. At physiological pH, oxyhemoglobin is a stronger acid than deoxyhemoglobin. This is due to the influence of iron-bound oxygen on the affinity of the nearest imidazole groups of histidine to hydrogen ions. During release from oxygen in the tissues, hemoglobin acquires a great ability to bind protons, and the reverse processes occur in the lungs.

Adult hemoglobin HbA contains 4 hemes, each of which is “wrapped” by one polypeptide chain. The protein part of the molecule – globin – consists of four polypeptide chains: two α-chains – 141 amino acid residues each and two β-chains – 146 amino acid residues each (574 amino acids in total).

In the blood of an adult, in addition to the main hemoglobin HbA1, there is hemoglobin HbA2, which migrates at a lower speed during electrophoresis, consisting of two α-chains and two δ-chains.

HbA2 accounts for about 2.5% of all hemoglobin. In addition, fetal hemoglobin (hemoglobin of newborns) is known – HbF, consisting of two α-chains and two γ-chains, which differs from HbA1 not only in the composition of amino acids, but also in physicochemical properties (oxygen affinity, spectral parameters, electrophoretic mobility, resistance to alkaline denaturation, etc.). The blood of a newborn contains up to 80% of HbF, but by the end of the first year of life it is almost completely replaced by HbA (in the blood of an adult, up to 1.5% of HbF from the total amount of hemoglobin).

Diseases hemoglobins (more than 200) are called hemoglobinoses. It is customary to divide them into *hemoglobinopathies* and other diseases.

About 150 different hemoglobinopathies have been described in humans, which are the result of mutations that lead to the replacement of one amino acid by another in the α or β polypeptide chains of the hemoglobin molecule. In most cases, an acidic amino acid is replaced by a basic or neutral one, so the formed hemoglobin differs from the normal one in terms of charge and electrophoretic mobility.

A classic example of hereditary hemoglobinopathies is sickle cell anemia, which is widespread in the countries of South America, Africa, and Southeast Asia.

The chemical defect of this pathology is the replacement in the β-chains of the hemoglobin S (HbS) molecule in the 6th position from the N-end of glutamic acid to valine. After giving up oxygen in the tissues, hemoglobin S turns into poorly soluble deoxyform and begins to precipitate in the form of spindle-shaped crystalloids called tactoids. The latter deform the cell and lead to massive hemolysis.

In this pathology, erythrocytes take the shape of a sickle under conditions of low partial pressure of oxygen. The disease is acute and children who are homozygous for the mutant gene often die at an early age.

Thalassemia is a genetically determined violation of the synthesis of one of the normal chains of hemoglobin. If the synthesis of β-chains is inhibited, then β-thalassemia develops; with a genetic defect in the synthesis of α-chains, α-thalassemia develops.

With β-thalassemia, up to 15% of HbA2 appears in the blood along with HbA1, and the content of HbF increases sharply – up to 15-60%. The disease is characterized by hyperplasia and destruction of the bone marrow, damage to the liver, spleen, deformation of the skull and is accompanied by severe hemolytic anemia. Erythrocytes in thalassemia have a target-like shape.

Normal and pathological derivatives of hemoglobin

Of the variety of hemoglobin derivatives that are of undoubted interest, one should, first of all, point to oxyhemoglobin Hb-O_2. The addition of one oxygen molecule to the heme tetramer facilitates the addition of the next one, therefore the hemoglobin oxygen saturation curve has a sigmoidal shape, which indicates the cooperativity of oxygen binding. Cooperativeness ensures not only the binding of the maximum amount of oxygen in the lungs, but also the release of oxygen in peripheral tissues, which is also facilitated by the presence of H^+ and CO_2 in them.

In turn, oxygen accelerates the release of CO_2 and H^+ in the lung tissue. This allosteric dependence between the attachment of H^+, O_2 and CO_2 was named the Bohr effect.

Binding of CO_2 (formation of carbhemoglobin) occurs due to terminal α-amino groups with the formation of carbamate and the release of protons:

$$CO_2 + Hb\text{-}NH_3^+ \rightarrow Hb\text{-}NH\text{-}COO^- + 2H^+$$

In addition to oxygen and CO_2, hemoglobin easily combines with other gases, in particular with carbon monoxide (II), nitrogen oxides, etc. In case of carbon monoxide (II) poisoning, the latter strongly binds to hemoglobin, forming a very stable, extremely slowly dissociating complex – carboxyhemoglobin (Hb-CO), unable to tolerate oxygen, which leads to severe hypoxia, pronounced shortness of breath, cyanosis, tachycardia.

In case of poisoning by nitrites, nitrogen oxides, nitrobenzene vapors and other oxidizing agents, a part of hemoglobin is oxidized into methemoglobin (Hb-OH) – at the same time, Fe^{2+} of heme turns into Fe^{3+}. Methemoglobin is also incapable of transporting oxygen. At the same time, it binds cyanides very effectively, so some methemoglobin-forming agents (amyl and propyl nitrites, sodium nitrite, methylene blue, chromosmone) are used as antidotes when affected by hydrocyanic acid and its derivatives.

Low methemoglobinemia in healthy people (on average 0.83 ± 0.42% of the total hemoglobin content) is explained by the constant reduction of methemoglobin to oxyhemoglobin by a special methemoglobin-reductase system, which includes 2 subsystems: the main one – NADH-methemoglobin reductase (approximately 70% of the reducing activity) and auxiliary – NADPH-methemoglobin reductase (5-6% reducing activity). Another amount of methemoglobin is restored to oxyhemoglobin with the help of glutathione (9-12%) and ascorbic acid (12-16%). Auxiliary components of the methemoglobin reductase system are the enzymes catalase, superoxide dismutase, and glutathione peroxidase.

An increase in the level of blood glucose in diabetes leads to the formation of glycosylated hemoglobin (HbA1c). This indicator reflects the average blood sugar content over a long period (up to 3 months). A high content of glycosylated hemoglobin indicates a high level of glycemia in the last three months and a high risk of developing complications of diabetes.

Heme synthesis

Porphyrins are intermediate products in heme synthesis reactions. These are aromatic structures characterized by a high melting point and an intense color (most often dark red). Molecules of porphyrins are flat and usually associated due to the formation of hydrogen bonds.

Synthesis of the protoporphyrin ring is most active in hepatocytes and erythrocytes. At the first stage (in the mitochondria), δ-aminolevulinic acid is formed from glycine and the active form of succinic acid under the action of δ-aminolevulinate synthase (pyridoxal phosphate coenzyme). The activity of this enzyme is regulated according to the principle of negative feedback by the end product of synthesis – heme, the accumulation of which leads to a decrease in enzymatic activity.

The following stages of synthesis take place in the cytosol: cyclization of two molecules of δ-aminolevulinic acid gives a substituted pyrrole - porphobilinogen, the condensation of four molecules of which with the help of uroporphyrinogen-I synthase leads to the formation of two tetrapyrroles – uroporphyrinogen I and uroporphyrinogen III. Moreover, uroporphyrinogen-III cosynthase is needed for the synthesis of uroporphyrinogen III, from which heme is synthesized in several stages (through the formation of copro- and protoporphyrinogens). When the synthesis of this enzyme is genetically disrupted, a non-physiological isomer of uroporphyrinogen – uroporphyrinogen I is formed (pathology is erythropoietic porphyria or Gunther disease).

In the final stage (again in the mitochondria), protoporphyrin IX with the participation of the enzyme ferrochelatase (heme synthase) attaches an iron cation, the source of which is the iron-containing protein ferritin, forming heme.

Any enzymatic defect in the synthesis of heme that occurs at its various stages is the cause of the corresponding forms of porphyrias, manifested by acute neurological disorders or skin manifestations. Depending on the organ localization of the enzymatic defect, porphyrias are divided into hepatic and erythropoietic.

Acute hepatic porphyrias include three classic forms: acute intermittent porphyria, hereditary coproporphyria, and variegated porphyria. All of them are characterized by exacerbations with neuropsychiatric symptoms (convulsions, visual disturbances) and peripheral neuropathy, as well as vomiting, abdominal colic and acute abdominal pain, constipation.

The urine is red in color, a large amount of porphyrin precursors - δ-aminolevulinic acid and porphobilinogen are excreted in the urine.

The fourth form of hepatic porphyria - late cutaneous porphyria, may also be hereditary, although it may also be associated with damage to hepatocytes; acute neurological manifestations are not observed.

Erythropoietic porphyria includes congenital erythropoietic porphyria and erythropoietic protoporphyria. These porphyrias are characterized by red urine, caused by the accumulation of uroporphyrinogen I by the kidneys, which is converted into uroporphyrin I in the urine.

Hemoglobin breakdown in tissues and its disorders

In the body of a healthy person with a body weight of 70 kg, more than 108 erythrocytes are destroyed every hour, which is approximately 6 g of hemoglobin per day. The protein part of hemoglobin breaks down into amino acids.

Heme iron cations, combining with the transport protein transferrin, replenish iron reserves in the composition of the liver protein ferritin, and the porphyrin ring of heme breaks down into bile pigments (verdoglobin, biliverdin, bilirubins and pigments formed from bilirubin in the intestines).

The breakdown of hemoglobin begins mainly in Kupffer cells (liver) and cells of the reticuloendothelial system (RES) of the spleen. Formation of intermediate metabolites of hemoglobin breakdown (verdoglobin, biliverdin, bilirubin IXa) occurs in the liver and spleen, and bilirubin conjugation occurs only in hepatocytes.

The transformation of free (indirect) bilirubin, which is formed during the destruction of erythrocytes and the breakdown of hemoglobin in the organs of the

RES, into bound (conjugated or direct) bilirubin in the hepatocyte is carried out in three stages (fig. 3.2):

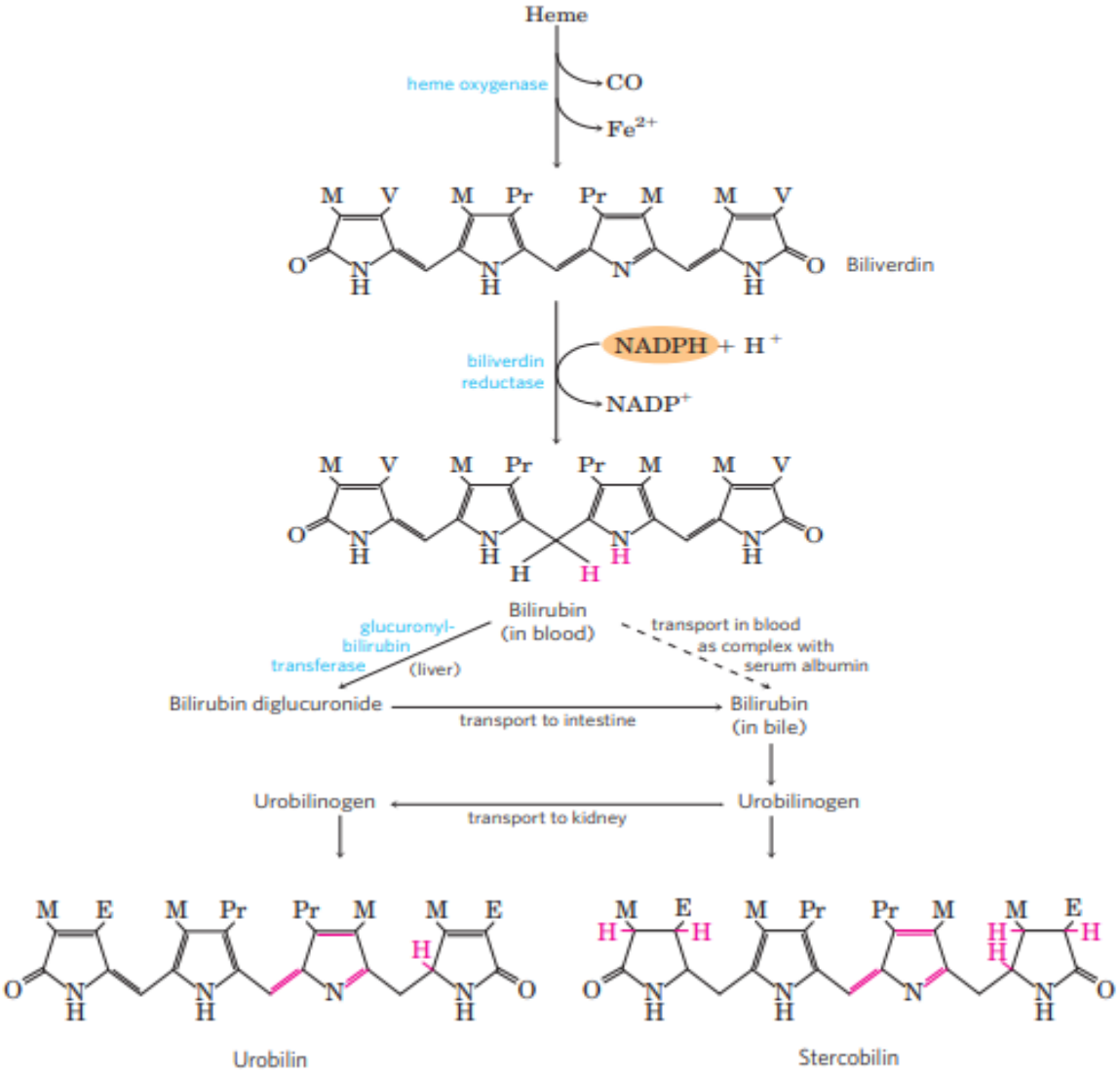


Fig. 3.2. Bilirubin and its breakdown product.

I stage is cleavage of albumin and uptake of indirect bilirubin by the liver cell.

II stage is formation of water-soluble bilirubin-diglucuronide by conjugation of bilirubin with 2 molecules of UDP-glucuronic acid.

The activity of UDP-glucuronyltransferase, which ensures the conjugation of bilirubin, is reduced in newborns, which, against the background of increased hemolysis due to the replacement of their HbF with HbA of adults, leads to the appearance of physiological jaundice of newborns or pathological jaundice (in case of Rhesus conflict, prematurity, etc.);

Stage III is release of the formed bound (direct) bilirubin from the liver cell into the bile ducts.

The content of total bilirubin is normal – no more than 20.5 μmol / l.

Further metabolism of bilirubin is associated with its entry into the bile ducts and intestines where, under the influence of microflora, bilirubin is gradually restored to mesobilinogen.

Part of the mesobilinogen is absorbed in the intestines (urobilinogen) and through the portal vein system again enters the liver, where it is normally almost completely destroyed into pyrroles. The main amount of mesobilinogen enters the large intestine and is reduced to stercobilinogen, which in the lower parts of the large intestine (mainly in the rectum) is oxidized to stercobilin and excreted with feces, determining itcoloring in healthy people. A small part of stercobilinogen enters the blood through the hemorrhoidal veins and is excreted in the urine.

The mechanism of occurrence and clinical and laboratory criteria for diagnosing jaundice

Violation of the breakdown of hemoglobin manifests itself as a number of distinct by nature pigment metabolism disorders, the assessment of which is of crucial importance in the differential diagnosis of jaundice (parenchymal, mechanical and hemolytic).

Parenchymal (hepatic) jaundice occurs when the liver parenchyma is damaged in patients with hepatitis, cirrhosis, cancer and other liver diseases. At the same time, free bilirubin uptake by the liver cell and its binding to glucuronic acid is disrupted, which leads to an increase in free (indirect) bilirubin in the blood plasma. Violation of the secretion of bilirubin-diglucuronide (direct bilirubin) from the liver cell into the bile capillaries leads to the regurgitation of bile back into the sinusoids and into the general bloodstream and, accordingly, to an increase in the content of *bound (direct) bilirubin* in the blood.

Violation of hepatocyte function is also accompanied by the loss of their ability to capture and metabolize mesobilinogen (urobilinogen) absorbed in the

intestine, which in large quantities enters the general bloodstream and is excreted in the urine in the form of *urobilin*.

Thus, with parenchymal jaundice, the content of both free (indirect) and bound (direct) bilirubin in the blood is increased. The latter is a well-soluble compound in water, easily passes the kidney barrier and appears in urine, causing its dark color ("dark beer color"). Urobilin is also present in large quantities in urine. In feces, the content of stercobilin may be slightly reduced due to impaired bile secretion by hepatocytes.

In addition, the death of hepatocytes leads to an increase in the concentration of transaminases in the blood, primarily alanine aminotransferase (ALT).

Mechanical (obstructive, subhepatic) jaundice develops when the extrahepatic biliary tract is obstructed by a stone or the common bile duct is compressed by a tumor (cancer of the head of the pancreas, metastases of cancer to the lymph nodes of the portal of the liver).

As a result, the release of bile into the intestines is blocked and, accordingly, *urobilinogen (mesobilinogen and stercobilinogen)* is not formed.

In this regard, urobilin in the urine and stercobilin in the feces are completely absent (steatorrhea – faecal and acholic (discolored) feces). The level of bound (direct) bilirubin in the blood increases significantly, since its formation by the liver cell has not been disturbed for a long time. Accordingly, a large amount of bound bilirubin appears in the urine and the urine acquires a dark color ("beer color").

Confirmation of the diagnosis is an increase in the concentration of alkaline phosphatase and γ-glutamyltransferase in the blood.

With hemolytic (suprahepatic) jaundice, an excessive amount of free (indirect) bilirubin is formed in the cells of the RES, which does not have time to be fully metabolized in the liver, although the function of hepatocytes is not disturbed and they work with increased load.

As a result, the content of free (indirect) bilirubin in the blood increases, which does not pass the kidney barrier and does not enter the urine.

Since the amount of bound (direct) bilirubin released by the liver into the intestines (and, accordingly, stercobilinogen) also increases significantly, the level of urobilin in the urine is significantly increased, which enters the general bloodstream through the hemorrhoidal veins.

Unlike parenchymal and obstructive jaundice, the activity of all the above-mentioned enzymes in the blood does not change in this case.

The main laboratory indicators of parenchymal, mechanical and hemolytic jaundice are presented in the table 3.1.

Table 3.1

Laboratory indicators		**Types of jaundice**	
		mechanical	hemolytic
Blood bilirubin	Parenchymatous Direct and indirect increased	Direct elevated	Indirect elevated
Urine bilirubin Urobilin urine Fecal stercobilin	+	+	-
	mesabilinogen	-	stercobilinogen
	+	-	+

2. TASKS FOR INDEPENDENT WORK.

In the table with test tasks, underline the key words, choose the correct answer and justify it:

1.	In the group of children who ate sweet juicy watermelon, two showed signs of poisoning: sharp weakness, dizziness, headache, vomiting, shortness of breath, tachycardia,	

	bluishness of lips, ears, fingertips. Laboratory analysis of the watermelon showed a high content of nitrates. What is the leading mechanism in the pathogenesis of poisoning in only two children? A. Blockade of cytochrome oxidase B. Deficiency of superoxide dismutase C. Insufficiency of met-Hb-reductase D. Insufficiency of glutathione peroxidase E. Catalase deficiency	
2.	A 1.5-year-old child was brought to the reception department with signs of nitrate poisoning: persistent cyanosis, shortness of breath, convulsions. What pathogenetic mechanism underlies these symptoms? A. Formation of methemoglobin B. Formation of oxyhemoglobin C. Formation of carbhemoglobin D. Formation of carboxyhemoglobin E. Formation of reduced hemoglobin	
3.	A 52-year-old patient has been	

	troubled by attacks of pain in the right hypochondrium for several days after eating fatty food. Yellowing of the sclera and skin, acholic stool, "beer-colored" urine is visually determined. The presence of which substance in the patient's urine caused the dark color of urine in obturative jaundice? A. Ketone bodies B. Glucose C. Sterkobilin D. Urobilin E. Bilirubinglucuronide	
4.	The patient has an increased sensitivity of the skin to sunlight. His urine acquires a dark red color when standing for a long time. What is the most likely cause of this condition? A. Porphyria B. Alkaptonuria C. Albinism D. Pellagra E. Hemolytic jaundice	
5.	After repairing the car in the garage,	

	the driver was taken to the hospital with symptoms of gas poisoning. The content of which substance in the blood will be increased? A. Carboskyhemoglobin B. Carbhemoglobin C. Glycosylated hemoglobin D. Oxyhemoglobin E. Methemoglobin	
6.	The patient's long-term consumption of contaminated vegetables and fruits led to nitrate poisoning. What derivative of hemoglobin was formed in the blood of this patient? A. Hb CN B. Hb-OH C. Hb O^2 D. Hb CO E. Hb NHCOOH	
7.	A patient suffering from congenital erythropoietic porphyria has skin photosensitivity. This is due to the accumulation of which compound in the skin?	

	A. Heme B. Uroporphyrinogen I C. Uroporphyrinogen II D. Protoporphyrin E. Coproporphyrinogen III	
8.	When studying the primary structure of the globin molecule, the replacement of glutamic acid with valine was found. What hereditary pathology is this characteristic of? A. Thalassemia B. Hereditary spherocytosis C. Sickle cell anemia D. Hemoglobinosis E. Favism	
9.	A 20-year-old patient complains of general weakness, dizziness, and rapid fatigue. In the blood: Hb – 80 g/l. Microscopically: erythrocytes of a changed shape. The reason for this condition can be: A. Sickle cell anemia B. Acute intermittent porphyria C. Addison's disease D. Parenchymatous jaundice E. Obstructive jaundice	

10.	The patient, who consulted a doctor, has yellow skin, dark urine, and dark yellow feces. An increase in the concentration of which substance will be observed in the blood serum? A. Mesobilirubin B. Conjugated bilirubin C. Biliverdin D. Free bilirubin E. Verdoglobin	
11.	A person has diabetes mellitus, which is accompanied by fasting hyperglycemia of more than 7.2 mmol / l. The level of which blood plasma protein allows retro-prospective (for the previous 4-8 weeks before the examination) to assess the level of glycemia? A. Glycosylated hemoglobin B. Ceruloplasmin C. C-reactive protein D. Fibrinogen E. Albumin	
12.		

	A 48-year-old patient was admitted to the clinic with complaints of weakness, irritability, and sleep disturbances. Objectively: skin and sclera are yellow; increased content of total bilirubin in the blood with a predominance of direct; acholic stool; dark urine (bile pigments). What type of jaundice is observed in the patient: A. Gilbert syndromea B. Crigler–Najjar syndrome C. Hemolytic D. Parenchymatous E. Mechanical	
13.	The mother turned to the doctor about the fact that a 5-year-old child develops erythema, vesicular rash, and skin itching under the influence of sunlight. Laboratory studies revealed a decrease in iron in the blood serum, an increase in the excretion of uroporphyrinogen I in the urine. The most likely hereditary pathology in the child is: A. Coproporphyria B. Erythropoietic porphyria	

	C. Hepatic porphyria D. Methemoglobinemia E. Intermittent porphyria	
14.	A 42-year-old patient developed yellowness of the skin, sclera, and mucous membranes. In blood plasma, the level of total bilirubin is elevated, in feces - stercobilin, and in urine - urobilin. What type of jaundice does the patient have? A. Obturational B. Cholestatic C. Gilbert disease D. Hemolytic E. Parenchymatous	
15.	For the treatment of jaundice, the appointment of barbiturates, which induce the synthesis of UDP - glucuronyltransferase, is indicated. The therapeutic effect is due to the formation of: A. Protoporphyrin B. Biliverdin C. Heme D. Indirect bilirubin	

	E. Direct (conjugated) bilirubin	
16.	A patient with jaundice has an increased content of direct bilirubin and bile acids in the blood; there is no stercobilinogen in the urine. With which jaundice is possible the presence of these signs? A. Hepatic B. Hemolytic C. Suprahepatic D. Parenchymatous E. Mechanical	
17.	The patient was admitted to the clinic with complaints of general weakness and sleep disturbances. The skin is yellow. In the blood: increased amount of direct bilirubin, bile acids, acholic stool. For which condition are these changes characteristic? A. Gilbert syndrome B. Chronic cholecystitis C. Mechanical jaundice D. Adrenal jaundice E. Hemolytic jaundice	

18.	In a patient with jaundice, it was established: an increase in the content of total bilirubin in the blood plasma due to indirect, in the feces and urine - a high content of stercobilin, the level of direct bilirubin in the blood plasma is within the normal range. What type of jaundice can you think of? A. Mechanical B. Jaundice of newborns C. Gilbert disease D. Parenchymatous E. Hemolytic	
19.	The patient is 33 years old, has been ill for 10 years. He periodically goes to the doctor with complaints of acute abdominal pain, convulsions, and visual disturbances. His relatives have similar symptoms. Urine is red. Hospitalized with a diagnosis of acute intermittent porphyria. The cause of the disease may be a violation of biosynthesis: A. Prostaglandins B. Insulin	

	C. Bile acids D. Collagen E. Heme	
20.	In the 1970s, scientists established that the cause of severe jaundice in newborns is a violation of bilirubin binding in hepatocytes. What substance is used to form the conjugate? A. Uric acid B. Sulfuric acid C. Glucuronic acid D. Pyruvic acid E. Lactic acid	
21.	A premature baby has jaundice. What enzyme is it related to? A. Acid phosphatase B. Catalases C. NAD + - dehydrogenases D. Alkaline phosphatase E. UDP- transglucuronidases	
22.	In a 20-year-old patient, it was established: an increase in the	

	content of total bilirubin in the blood plasma due to indirect (free), high content of stercobilin in the feces and urine, the level of direct bilirubin in the blood plasma is within the normal range. What type of jaundice can you think of? A. Mechanical B. Parenchymatous (hepatic) C. Jaundice of newborns D. Gilbert disease E. Hemolytic	
23.	The patient has an increased sensitivity of the skin to sunlight, and when standing, the urine acquires a dark red color. What disease is this characteristic of? A. Albinism. B. Alkaptonuria. C. Hemolytic jaundice. D. Pellagra. E. Porphyria.	
24.	A 46-year-old woman suffering from gallstone disease developed jaundice. At the same time, the urine became dark yellow, and the feces became discolored. Indicate the	

	concentration of which substance in the blood serum will increase to the greatest extent? A. Biliverdin. B. Free bilirubin. C. Conjugated bilirubin. D. Mesobilirubin. E. Urobilinogen.	
25.	After a blood transfusion, the patient has jaundice of the skin and mucous membranes, an increased level of total and indirect bilirubin in the blood, an increased level of urobilin in the urine, and a level of stercobilin in the feces. What type of jaundice is this? A. Hemolytic jaundice. B. Jaundice of newborns. C. Obstructive jaundice. D. Parenchymal jaundice. E. Hereditary jaundice.	
26.	In the 1970s, scientists established that the cause of severe jaundice in newborns is a violation of bilirubin binding in hepatocytes. What	

	substance is used to form the conjugate? A. Glucuronic acid. B. Lactic acid. C. Uric acid. D. Sulfuric acid. E. Pyruvic acid.	
27.	In a patient with jaundice, an increase in total bilirubin was found in the blood due to its indirect fraction. Urine and feces are intensely colored. What is the most likely mechanism of these violations? A. Increased hemolysis of erythrocytes. B. Violation of urobilinogen conversion in the liver. C. Violation of formation of direct bilirubin. D. Damage to the liver parenchyma. E. Complex condition of bile outflow from the liver	
28.	In case of enzymatic jaundice, there is a violation of the activity of the UDP-glucuronyl transferase enzyme. Indicate which compound	

	accumulates in blood serum in these pathologies. A. Biliverdin. B. Verdoglobin. C. Mesobilirubin. D. Indirect bilirubin. E. Direct bilirubin.	
29.	A patient with pronounced yellowness of the skin, sclera, and mucous membranes was admitted to the clinic. Urine analysis showed the presence of direct bilirubin in it. Urine is the color of dark beer, the number of bile pigments in feces is reduced. What type of jaundice is observed in the patient? A. Absorption. B. Hemolytic. C. Conjugation. D. Obturational. E. Physiological.	
30.	As a result of the transfusion of Rh incompatible blood, the patient developed hemolytic jaundice. What laboratory blood test confirms this type of jaundice?	

	A. Reduction in the content of conjugated bilirubin. B. Decrease in the content of unconjugated Bilirubin. C. Reduction of stercobilin content. D. Accumulation of unconjugated bilirubin. E. Accumulation of urobilinogen.	
31.	The patient complains of yellowness of the skin, itching of the skin, general weakness. Urine: absent urobilin. What is the patient's pathology? A. Hemolytic jaundice. B. Acute liver failure C. Mechanical jaundice. D. Parenchymal jaundice. E. Chronic liver failure.	
32.	The patient developed yellowness of the skin, sclera and mucous membranes. In blood plasma, the level of total bilirubin is elevated, in feces - stercobilin, in urine - urobilin. What type of jaundice does the patient have? A. Hemolytic. B. Obturational.	

	C. Parenchymatous. D. Gilbert disease. E. Cholestatic.	
33.	A patient with jaundice has an increased content of direct bilirubin and bile acids in the blood, and there is no stercobilinogen in the urine. In which type of jaundice is it possible to have these signs? A. Hemolytic. B. Mechanical. C. Suprahepatic. D. Parenchymatous. E. Hepatic.	

3. LITERATURE. See page 320.

LESSSON №4

4. TOPIC: CLASSIFICATION AND PROPERTIES OF HORMONES. MECHANISM OF ACTION OF PROTEIN-PEPTIDE HORMONES AND BIOGENIC AMINES

1. INFORMATION MATERIAL.

The human body exists as a whole thanks to a system of internal connections that ensure the transfer of information from one cell to another in the same tissue or between different tissues. Without this system, it is impossible to maintain homeostasis. In the transmission of information between cells in multicellular living organisms, three systems are involved: the central nervous system (CNS), the endocrine system (glands of internal secretion) and the immune system.

The methods of information transmission in all the named systems are chemical. Mediators in the transmission of information can be signaling molecules.

Such signaling molecules include four groups of substances: endogenous biologically active substances (mediators of the immune response, growth factors, etc.), neurotransmitters, antibodies (immunoglobulins) and hormones.

Properties of hormones

High biological activity. The concentration of hormones in the blood is very small, but their action is strongly expressed, so even a small increase or decrease in the hormone level in the blood causes various, often significant deviations in the metabolism and functioning of organs and can lead to pathology.

Short life time. Usually from several minutes to half an hour, after which the hormone is inactivated or destroyed. But with the destruction of the hormone, its action does not stop, but can last for hours and even days.

Action distance. Hormones are produced in some organs (endocrine glands) and act in others (target tissues).

High specificity of action. The hormone acts only after binding to the receptor. The receptor is a complex protein-glycoprotein consisting of protein and

carbohydrate parts. The hormone binds precisely to the carbohydrate part of the receptor. Moreover, the structure of the carbohydrate part has a unique chemical structure and corresponds to the spatial structure of the hormone. Therefore, the hormone unmistakably, precisely, specifically binds only to its receptor, despite the low concentration in the blood.

Not all tissues respond to the hormone in the same way. Those tissues that have receptors for this hormone have a high sensitivity to the hormone. In such tissues, it causes the most pronounced shifts in metabolism and functions. If there are receptors for the hormone in many or almost all tissues, then it has a general effect (thyroxine, glucocorticoids, somatotropic hormone, insulin). If receptors for a hormone are present in a very limited number of tissues, then such a hormone has a selective effect. Tissues that have receptors for this hormone are called target tissues. In target tissues, hormones can affect the genetic apparatus, membranes, and enzymes.

Classification of hormones

By chemical nature hormones are divided into the following groups:

1. peptide - hormones of the hypothalamus and pituitary gland, insulin, glucagon, hormones of the parathyroid glands;

2. derivatives of amino acids - adrenaline, thyroxine;

3. steroid - glucocorticoids, mineralocorticoids, male and female sex hormones;

4. eicosanoids - hormone-like substances that have a local effect; they are derivatives of arachidonic acid (a polyunsaturated fatty acid).

By place of formation hormones are divided into hormones of the hypothalamus, pituitary gland, thyroid gland, parathyroid glands, adrenal glands (cortical and medulla), female sex hormones, male sex hormones, local or tissue hormones.

By influence on biochemical processes and functions hormones are divided into:

1. hormones that regulate metabolism (insulin, glucagon, adrenaline, cortisol);

2. hormones that regulate the exchange of calcium and phosphorus (parathyroid hormone, calcitonin, calcitriol);

3. hormones that regulate water-salt exchange (aldosterone, vasopressin);

4. hormones regulating reproductive function (female and male sex hormones);

5. hormones that regulate the functions of endocrine glands (adrenocorticotropic hormone, thyroid-stimulating hormone, luteinizing hormone, follicle-stimulating hormone, somatotropic hormone);

6. stress hormones (adrenaline, glucocorticoids, etc.).

Mechanisms of hormone action

Hormones affect target cells. Target cells are cells that specifically interact with hormones using special receptor proteins. These receptor proteins are located on the outer membrane of the cell, in the cytoplasm, or in the nucleus.

Any receptor protein consists of at least two domains (sections) that provide two functions:

- “recognition” of the hormone;
- transformation and transmission of the received signal to the cell.

One of the domains of the receptor protein has a region complementary to some part of the signaling molecule. The process of receptor binding to a signal molecule is similar to the process of formation of an enzyme-substrate complex and is determined by the value of the affinity constant.

Most receptors have not been studied enough, because their isolation and purification are very complex processes. In addition, the content of each type of receptor in the cells is very low. But it is known that hormones interact with their receptors in a physicochemical way. Electrostatic and hydrophobic interactions are formed between the hormone molecule and the receptor. When the receptor binds to the hormone, conformational changes occur in the receptor protein, and the complex of the signal molecule with the receptor protein is activated. In an active state, it can

cause specific intracellular reactions in response to a received signal. If the synthesis or the ability of receptor proteins to bind to signal molecules is disturbed, diseases occur – endocrine disorders. There are three types of such diseases:

1. Changes associated with insufficient synthesis of receptor proteins.
2. Associated with a change in the structure of the receptor - genetic defects.
3. Associated with the blocking of receptor proteins by antibodies.

There are two main methods of signal transmission in the target cell from signal molecules with a membrane mechanism of action:

1. adenylate cyclase or guanylate cyclase systems.
2. phosphoinositide system.

Adenylate cyclase system

Main components: membrane protein-receptor (R), G-protein, enzyme adenylate cyclase (AC), guanosine triphosphate, protein kinases. In addition, ATP is required for the normal functioning of the adenylate cyclase system (fig. 4.1).

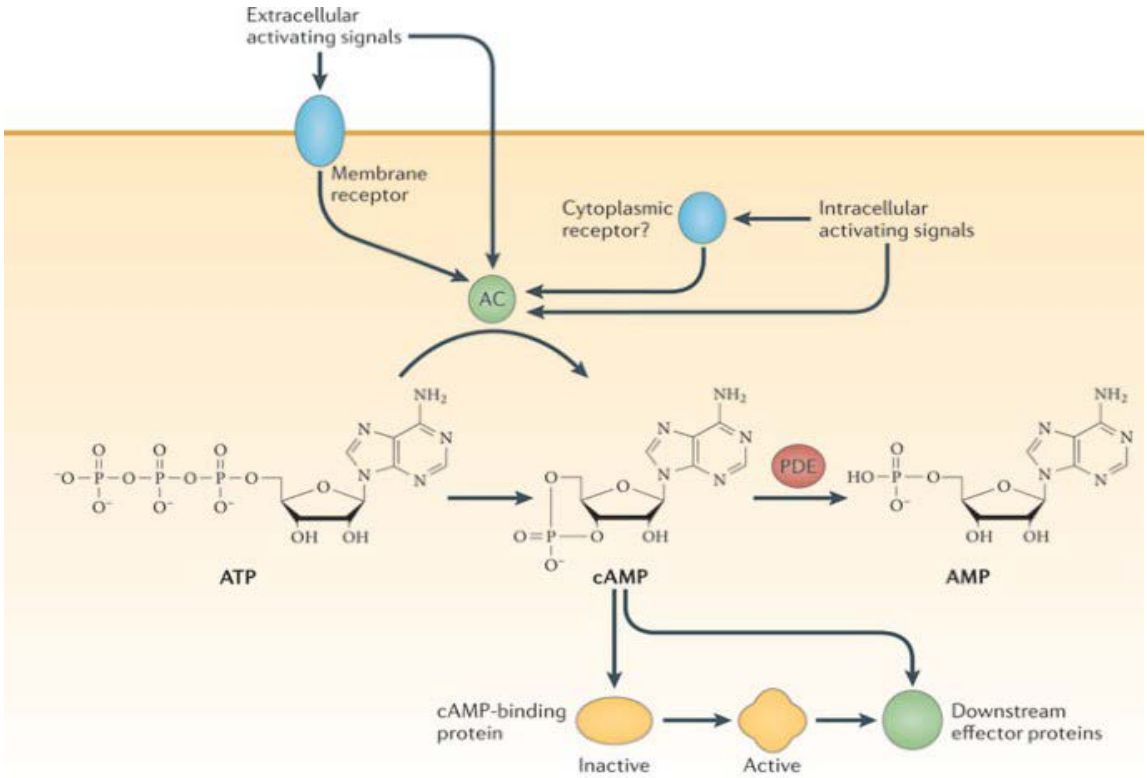


Fig. 4.1. Scheme of signal transmission to target cells using the adenylate cyclase system

As can be seen from the figure, the receptor protein, G-protein, next to which GTP and the enzyme (adenylate cyclase) are located are embedded in the cell membrane.

Until the hormone acts, these components are in a dissociated state, and after the formation of a signal molecule complex with the receptor protein, changes in the conformation of the G-protein occur. As a result, one of the G-protein subunits acquires the ability to bind to GTP.

The “G-protein-GTP” complex activates adenylate cyclase. Adenylate cyclase begins to actively convert ATP molecules into c-AMP.

c-AMP has the ability to activate special enzymes - protein kinases (protein kinase A) consist of two P - regulatory and two K - catalytic subunits, which catalyze the phosphorylation reactions of various proteins with the participation of ATP. 4 cAMP molecules bind to the P subunit of protein kinase and bring it into an active state through conformational changes (fig. 4.2).

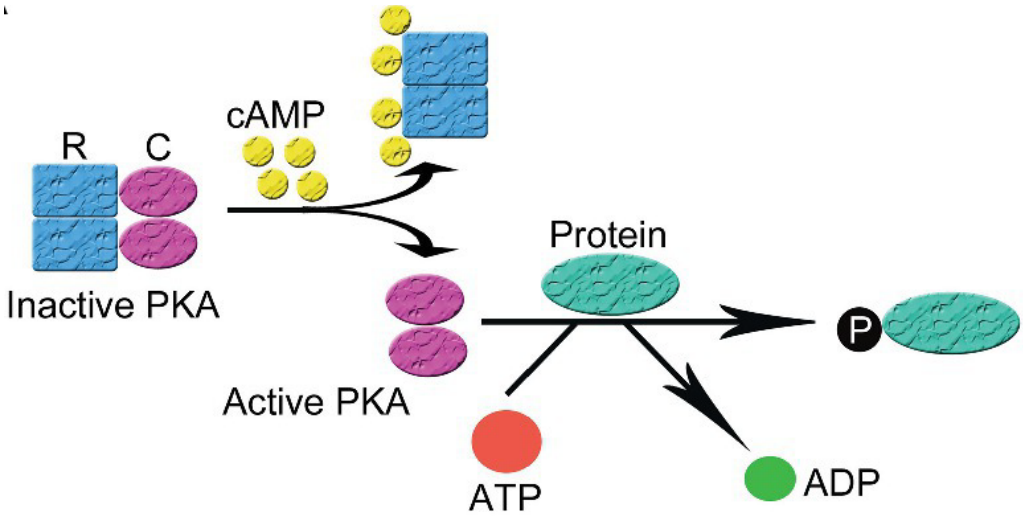


Fig. 4.2. Scheme of the mechanism of protein kinase activation

At the same time, residues of phosphoric acid are included in the composition of protein molecules. The main result of this phosphorylation process is a change in the activity of the phosphorylated protein. In different types of cells, proteins with different functional activity undergo phosphorylation as a result of activation of the adenylate cyclase system. For example, it can be enzymes, nuclear proteins,

membrane proteins. As a result of the phosphorylation reaction, proteins can become functionally active or inactive.

Such processes will lead to changes in the rate of biochemical processes in the target cell.

Activation of the adenylate cyclase system lasts for a very short time, because G-protein after binding with adenylate cyclase begins to show GTPase activity. After the hydrolysis of GTP, the G-protein restores its conformation and ceases to activate adenylate cyclase. As a result, the cAMP formation reaction stops.

In addition to the members of the adenylate cyclase system, some target cells contain receptor proteins associated with G-proteins that lead to the inhibition of adenylate cyclase. At the same time, the “GTP-G-protein” complex inhibits adenylate cyclase.

When cAMP formation stops, phosphorylation reactions in the cell do not stop immediately: as long as cAMP molecules continue to exist, the process of protein kinase activation will continue. In order to stop the action of cAMP, there is a special enzyme in the cells – phosphodiesterase, which catalyzes the hydrolysis reaction of 3’, 5’-cyclo-AMP to AMP.

Some substances that have an inhibitory effect on phosphodiesterase (for example, alkaloids, caffeine, theophylline) contribute to maintaining and increasing the concentration of cyclo-AMP in the cell. Under the influence of these substances in the body, the duration of activation of the adenylate cyclase system increases, that is, the effect of the hormone increases. Hormones such as adrenaline, vasopressin, glucagon, calcitonin and a number of tropic hormones of the pituitary gland (ACTH, lipotropin, luteinizing hormone, etc.) act on the adenylate cyclase mechanism.

Adrenaline (the hormone of the medulla of the adrenal glands) is synthesized in the transamination reaction from norepinephrine. Methionine is used as a donor of labile methyl groups.

The guanylate cyclase system has a similar structure and mechanism of action.

In addition to the adenylate cyclase or guanylate cyclase systems, there is also a mechanism for transmitting information inside the target cell with the participation of calcium ions and inositol triphosphate.

Inositol triphosphate is a substance that is a derivative of a complex lipid – inositol phosphatide. It is formed as a result of the action of a special enzyme – phospholipase C, which is activated as a result of conformational changes in the intracellular domain of the membrane protein-receptor.

This enzyme hydrolyzes the phosphoester bond in the phosphatidyl-inositol-4,5-bisphosphate molecule, resulting in diacylglycerol and inositol triphosphate.

It is known that the formation of diacylglycerol and inositol triphosphate leads to an increase in the concentration of ionized calcium inside the cell. This leads to the activation of many calcium-dependent proteins inside the cell, including the activation of various protein kinases. And here, as with the activation of the adenylate cyclase system, one of the stages of signal transmission inside the cell is the phosphorylation of proteins, which leads to the physiological response of the cell to the action of the hormone.

A special calcium-binding protein – calmodulin – is involved in the work of the phosphoinositide signaling mechanism in the target cell. It is a low-molecular-weight protein (17 kDa), 30% of which consists of negatively charged amino acids (Gly, Asp) and is therefore capable of actively binding Ca+2. One molecule of calmodulin has 4 calcium-binding sites. After interaction with Ca+2, conformational changes of the calmodulin molecule occur and the Ca+2-calmodulin complex becomes able to regulate the activity (allosterically inhibit or activate) of many enzymes – adenylate cyclase, phosphodiesterase, Ca+2, Mg+2-ATPase and various protein kinases.

Tyrosine protein kinases - enzymes that phosphorylate specific proteins on tyrosine are divided into 2 types – membrane (receptor) and cytoplasmic. Intracellular tyrosine protein kinases are involved in the processes of signal transmission to the nucleus. Receptor tyrosine protein kinases are involved in transmembrane signal transmission.

Insulin receptor investigated in detail using biochemical methods and recombinant DNA technology. It is a heterodimer consisting of two subunits (α and β) in the alpha2-beta2 configuration, connected by disulfide bridges. Both subunits contain many glycosyl residues. Each of the glycoprotein subunits has a special structure and a specific function.

The catalytic center of tyrosine protein kinase is located on the intracellular domains of β-subunits. In the absence of the hormone, insulin receptors do not show tyrosine kinase activity. The addition of insulin to the binding center on α-subunits activates the enzyme, and the substrate is tyrosine protein kinase (β-subunits) itself, that is, the β-subunit is phosphorylated from several tyrosine residues. Phosphorylation of β-subunits occurs by the mechanism of intermolecular transphosphorylation, that is, one β-chain phosphorylates another β-chain of the same receptor molecule. This, in turn, leads to a change in the substrate specificity of tyrosine protein kinase; it is now able to phosphorylate other intracellular proteins. Activation and change in specificity are caused by conformational changes of the insulin receptor after hormone binding and autophosphorylation.

The key protein that phosphorylates tyrosine protein kinase is insulin receptor substrate-1 (IRS-I). Phosphorylated IRS-I activates enzymes such as tyrosine phosphoprotein phosphatase.

2. TASKS FOR INDEPENDENT WORK.

In the table with test tasks, underline the key words, choose the correct answer and justify it:

1	A 42-year-old man was admitted to the cardiology department with a diagnosis of angina pectoris. The complex of drugs prescribed to the patient includes a phosphodiesterase inhibitor. The concentration of which	

	substance in the heart muscle will increase? A. cAMP B. ATP C. ADP D. GMP E. AMP	
2	Inositol triphosphate in body tissues is formed as a result of hydrolysis of phosphatidylinositol diphosphates, which plays the role of a second messenger (messenger) in the mechanism of hormone action. Its influence in the cell is aimed at: A. Activation of adenylate cyclase B. Release of calcium ions from cellular depots C. Activation of protein kinase A D. Inhibition of protein kinase C E. Inhibition of phosphodiesterase	
3	A person for a long time consumed food poor in methionine, as a result of which he had a disorder of the functions of the nervous and endocrine systems. This could be caused by a violation of synthesis: A. Glucagon	

	B. Pyruvate	
	C. Tyronin	
	D. Fatty acids	
	E. Adrenaline	

3. LITERATURE. See page 320.

LESSON №5

5. TOPIC: MECHANISM OF ACTION AND EFFECT ON METABOLISM OF STEROID AND THYROID HORMONES. FORMATION AND FUNCTIONS OF EICOSANOIDS

1. INFORMATION MATERIAL.

The intracellular mechanism of action has:

- steroid hormones;

- derivatives of amino acids that are thyroxine and triiodothyronine.

These hormones regulate the rate of protein biosynthesis and have intracellular receptors. Steroid hormone receptors are localized in the cell cytosol, and thyroid hormone receptors are located in the nuclei of target cells. The formation of the hormone-receptor complex further affects gene expression and the rate of transcription in the cell. As a result, the number of synthesized molecules of certain proteins (enzymes) changes and the rate of metabolic processes changes (fig. 5.1.).

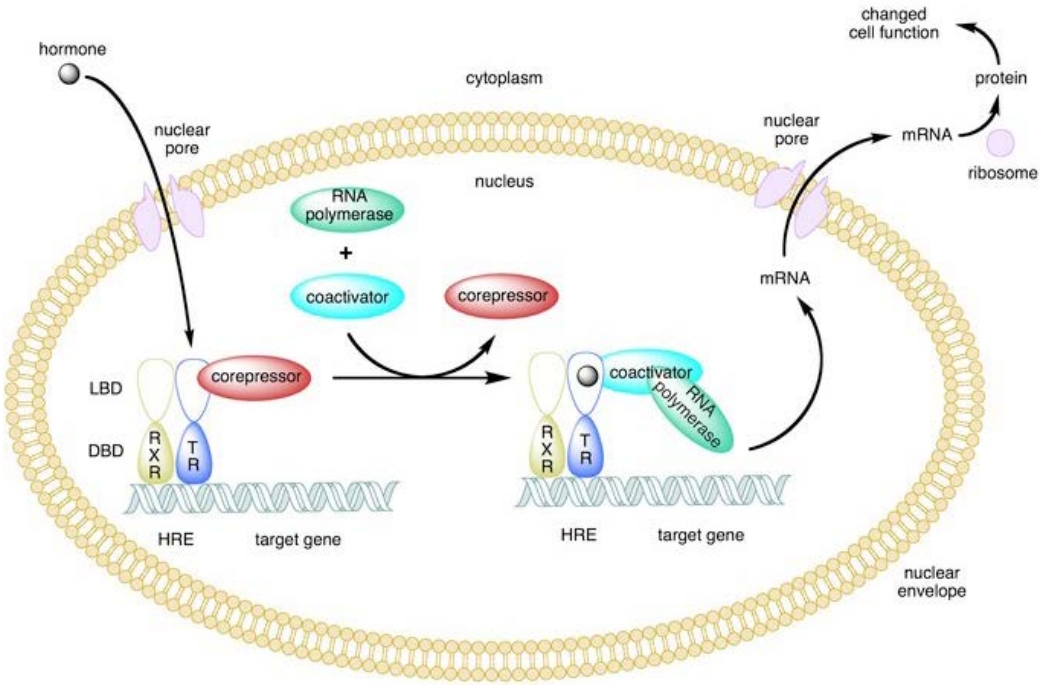


Fig. 5.1. General mechanism by which steroid and thyroid hormones regulate gene expression.

Hormones of the adrenal cortex

In the cortex of the adrenal glands, steroid hormones are formed from cholesterol: corticosteroids (glucocorticoids and mineralocorticoids) and sex hormones (female and male).

Biochemical features of the cortex of the adrenal glands

Per 1 gram of tissue, the adrenal cortex ranks second in the body after the brain in terms of cholesterol content and first in terms of ascorbic acid (vitamin C) content, which is necessary for the conversion of cholesterol into steroid hormones.

Disintegration of steroid hormones

Elimination of steroid hormones occurs in the liver in two ways.

1. About 90% of steroid hormones are first regenerated, then conjugated with glucuronic acid and easily excreted in the urine.

2. In 10% of glucocorticoids (fig. 5.2), mineralocorticoids and male (but not female) sex hormones, the side chain at the 17th carbon atom is split off and oxidized to form a keto group, resulting in the formation of 17-ketosteroids (17-CS), which are also secreted with urine in the form bound to glucuronic acid. Thus, 17-CS are not hormones, but the breakdown products of hormones: glucocorticoids, mineralocorticoids, and male (but not female) sex hormones.

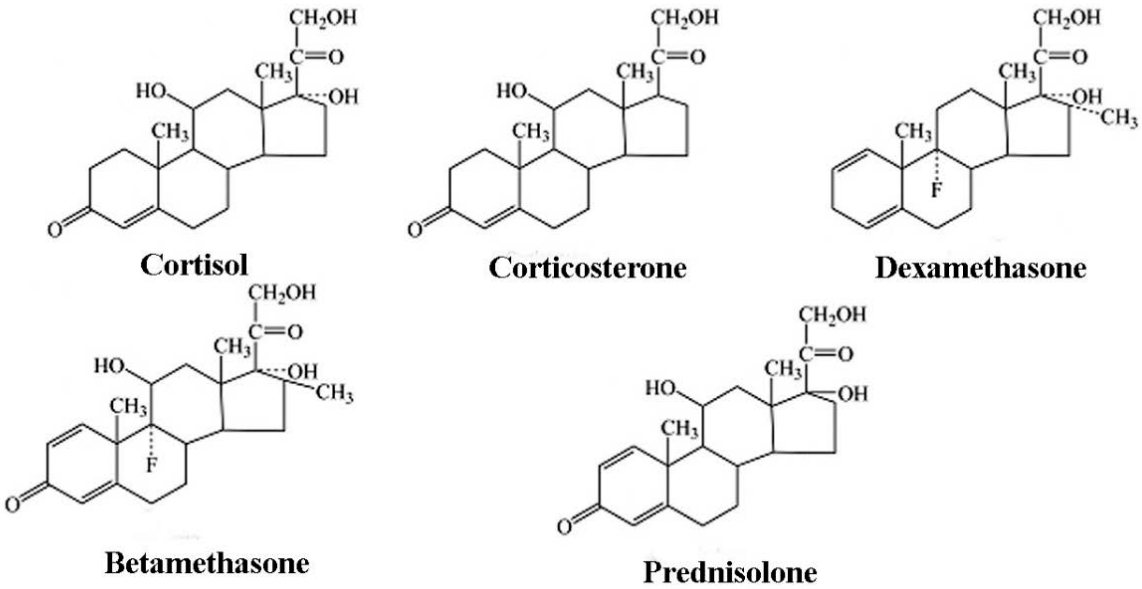


Fig. 5.2. The structural formulas of natural (cortisol, cortocosterone) and synthetic glucocorticoids.

Target tissues for this group of hormones: liver, muscles, adipose, lymphoid and connective tissues. Moreover, in the liver, glucocorticoids increase the permeability of membranes for the transport of substances into the cell and activate anabolic processes (i.e. synthesis of substances), and in other tissues – reduce the permeability of membranes and stimulate catabolism (i.e. the breakdown of substances).

Effect of glucocorticoids on metabolism

Carbohydrate metabolism. In all target tissues, glucocorticoids inhibit glycolysis. In the liver, hormones enhance gluconeogenesis and glycogen synthesis, in other tissues – reduce glucose transport into the cell, in muscles – reduce glycogen synthesis.

Due to an excess of glucocorticoids (the use of them for treatment in large doses or over a long period of time, as well as increased formation of glucocorticoids in the body), hyperglycemia develops due to the activation of gluconeogenesis in the liver and a decrease in the utilization of glucose in peripheral tissues. Prolonged hyperglycemia can lead to disruption of the insular apparatus of the pancreas and the development of steroid diabetes.

Lipid metabolism. In the liver, glucocorticoids increase the synthesis of triglycerides, very low-density lipoproteins (VLDL), and ketone bodies. In adipose tissue, hormones increase the breakdown of fat on the extremities, but increase the deposition of fat on the trunk and face. Therefore, with an excess of glucocorticoids, the so-called spider-like obesity and an increase in the level of ketone bodies in the blood are observed.

Protein metabolism. In the liver, glucocorticoids increase protein synthesis, in other tissues they decrease synthesis and stimulate the breakdown of tissue proteins. In this regard, with an excess of glucocorticoids, a slowdown in wound healing, muscle atrophy and weakness is observed, and in the bones – osteoporosis (thinning of the bone, which is accompanied by fractures that easily occur, for example, compression fractures of vertebrae and long bones even with minimal trauma).

In the lymphoid tissue, an excess of glucocorticoids leads to inhibition of antibody synthesis and a decrease in the formation of lymphocytes, therefore, during stress (when a lot of glucocorticoids are synthesized), the body's immune defense decreases and susceptibility to infectious diseases increases. The specified mechanism of action of glucocorticoids on lymphoid tissue is the basis of their use during the treatment of allergies and during transplantation to suppress the reaction of rejection of the transplanted organ.

Systemic effect of glucocorticoids

1. Glucocorticoids increase the secretion of HCl in the stomach. The mechanism of their action is due to the fact that glucocorticoids inhibit the synthesis of prostaglandins, which reduce the secretion of HCl, therefore, with an excess of glucocorticoids in the body, steroid ulcers of the stomach can develop.

2. Glucocorticoids have an anti-inflammatory effect. They affect all stages of the inflammatory process, but especially strongly reduce the permeability of membranes and suppress the synthesis of prostaglandins, which are tissue factors of inflammation, so the use of glucocorticoids is possible for the treatment of inflammation.

3. Glucocorticoids reduce the increased reactivity of the body, that is, hypersensitivity, so they are used during the treatment of allergies, and in particular, anaphylactic shock.

4. Glucocorticoids increase the body's resistance to damage by factors (injuries, infections, intoxications, pain, cold, physical exertion, severe mental changes).

5. Glucocorticoids have a permissive effect, that is, they enhance the action of other hormones.

Mineralocorticoids

Representatives of mineralocorticoids are aldosterone and deoxycorticosterone (fig. 5.3).

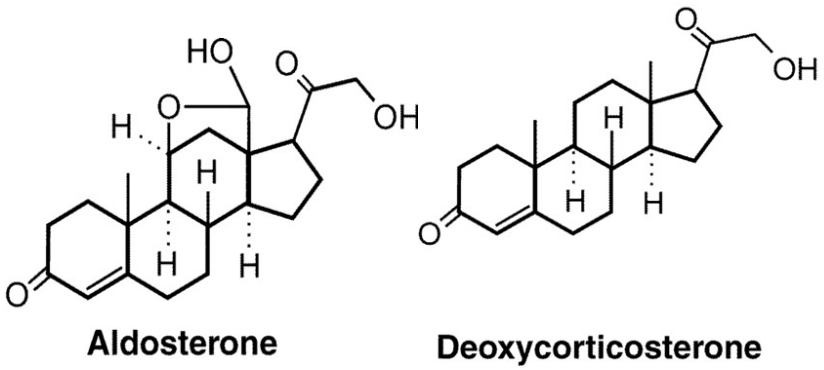


Fig. 5.3. The structural formulas of aldosterone and deoxycorticosterone

They regulate the exchange of sodium, potassium, chlorine and water (contribute to the retention of Na^+ and Cl^- ions in the body and the excretion of K^+ in the urine).

The main target tissue for the action of hormones is the epithelium of the distal tubules of the kidneys, where aldosterone increases the reabsorption of sodium from the urine into the blood. That is why aldosterone is called a sodium-retaining hormone. Since sodium “pulls” water along with it, with an excess of mineralocorticoids in the body, blood pressure rises, swelling and inflammatory processes intensify.

At the same time as sodium reabsorption increases under the influence of aldosterone, potassium excretion with urine increases. Therefore, with an excess of the hormone in the body, the concentration of potassium in the blood decreases, which leads to increased excitability of the myocardium, heart failure, severe weakness, characteristic changes on the ECG, and heart failure may develop.

Another target tissue for mineralocorticoids is sweat glands. In the heat, aldosterone prevents excessive excretion of sodium in sweat.

With insufficient synthesis of aldosterone, sodium is excreted in the urine, which leads to water loss, that is, dehydration of the body.

Glucocorticoids have a partial effect of mineralocorticoids, therefore, during long-term use of glucocorticoids for therapeutic purposes, patients must be prescribed potassium preparations.

Disruption of the hormonal function of the adrenal cortex

Hyperfunction of the adrenal cortex, or hypercorticism, can be manifested either by increased secretion of all groups of hormones, or mainly by one of the groups of hormones. In the latter case, 3 types of hypercorticism are distinguished.

1. Cushing's syndrome (tumor of the fascicular zone of the adrenal cortex, which synthesizes mainly cortisol) and Cushing's disease (non-neoplastic hyperplasia, i.e. growth of the adrenal cortex under the influence of excessive secretion of corticotropin by the pituitary gland).
2. Primary aldosteronism or Conn's disease – excessive formation of mineralocorticoids in the body (in the glomerular zone of the adrenal cortex).
3. Adrenal virilism or adrenogenital syndrome – accompanied by hypersecretion of male sex hormones in the reticular zone of the adrenal cortex. At the same time, the appearance of masculine features is observed in women, the strengthening of masculine features in men, and premature puberty in children.

Hypocorticism, called Addison's or bronze disease, is accompanied by a deficiency of gluco- and mineralocorticoids and mixed changes in metabolism and body functions. The cause of hypocorticism can be tuberculosis or atrophy of the cortex of the adrenal glands. Insufficient production of corticosteroids leads to severe weakness, fatigue, low blood pressure, skin pigmentation, craving for salty food, high sensitivity to stress and infections, inability to tolerate hunger due to severe hypoglycemia. The concentration of sodium in the blood decreases and the concentration of potassium increases.

Gonadal hormones

Female sex hormones

Female sex hormones are represented by estrogens and progestins (gestagens).

Estrogens (fig. 5.4) include: estradiol (formed in ovarian follicles), estriol (placental hormone) and estrone (synthesized in the cortex of the adrenal glands).

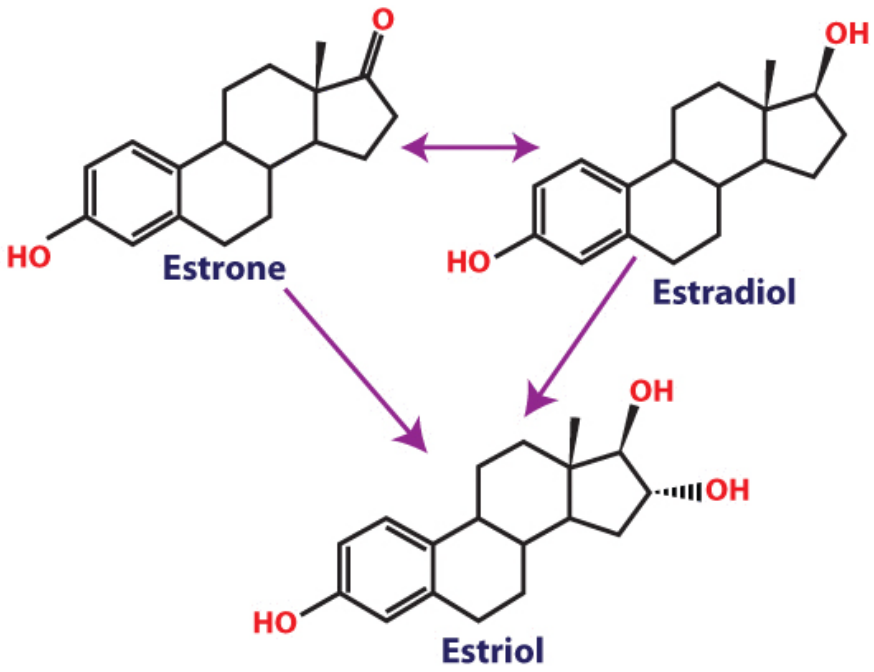


Fig. 5.4. The structural formulas of estradiol, estriol and estrone

A representative of progestins is progesterone, which is produced in the corpus luteum of the ovaries. A small amount of female sex hormones is also synthesized in the body of men.

Tissues sensitive to the action of estrogens are divided into 2 groups: sexual organs and non-sexual organs.

The effect of female sex hormones on the genitals

In the genitals, female sex hormones contribute to the development and functioning of these organs and the formation of secondary sexual characteristics during puberty.

In the uterus, the growth of the glandular epithelium of the endometrium and the smooth muscle tissue of the myometrium increases, the vascularization of the organ increases.

In the vagina, the number of cell layers increases, which is a diagnostic criterion for the effect of estrogens on the body.

In the mammary gland, estrogens stimulate the growth of ducts, progesterone – the growth of glandular tissue.

Effect of female sex hormones on non-sexual organs

In non-sexual organs, estrogens also have a characteristic effect.

Central nervous system, hypothalamus, pituitary gland – under the influence of hormones, the formation of typical sexual behavior, instinct, and psyche of a woman takes place.

Bones, cartilage, larynx – estrogens contribute to the formation of a characteristic “female” type of skeleton, larynx and voice. Estrogens accelerate the ossification of the epiphyses, where the bone growth zones are located, so if a girl has little estrogen during puberty, the ossification of the epiphyses slows down, and in this case the girl may be unusually tall. In adult women, with long-term administration of estrogens or their excessive formation in the body, intense calcification of bones occurs and the cavities in which the bone marrow is located may disappear, which leads to the development of anemia.

Skin – estrogens promote female-type hair growth, inhibit hair growth on the skin, reduce the secretory activity of the sebaceous glands (reduce oiliness of the skin).

Liver – estrogens stimulate the synthesis of specific liver proteins: angiotensinogen, which helps to increase blood pressure, and some blood coagulation factors (II, VII, IX, X). Therefore, with an excess of estrogens in the body, there is a tendency to hypertension and thrombosis.

In addition, estrogens, by their effect on the liver, increase the formation of very low-density lipoproteins (VLDL) and high-density lipoproteins (HDL) in it. VLDL consists of approximately 50% triglycerides (neutral fat), from the liver they are transported through the blood to adipose tissue, where fat is deposited. Therefore, in women, the muscles are always covered with a layer of subcutaneous fat. HDLs reduce the concentration of cholesterol in the blood, contribute to its removal from

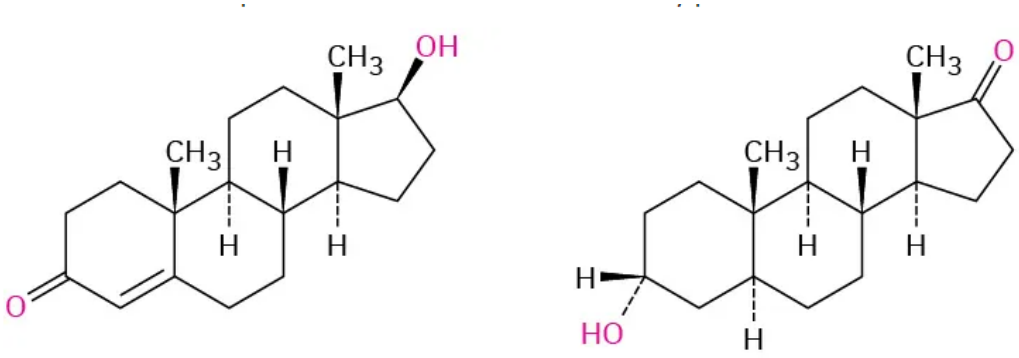
the body. Therefore, women suffer from atherosclerosis and myocardial infarction less often than men.

Adipose tissue – in it, estrogens and progesterone increase the synthesis of fat, inhibit its splitting, and contribute to the formation of typically female fat deposits.

Kidneys – estrogens contribute to the retention of sodium in the body, progesterone increases the loss of sodium in the urine. Since a lot of progesterone is produced during pregnancy, sodium is strongly excreted by the body, hence the craving for salty food.

Male sex hormones

Male sex hormones (androgens) are represented by testosterone and androsterone.



Testosterone **Androsterone**

Fig. 5.5. The structural formulas of testosterone and androsterone

They are formed in the testicles, the cortex of the adrenal glands, and the prostate gland. A small amount of androgens is synthesized in women in the ovaries. Like female sex hormones, androgens act not only on sexual, but also on non-sexual organs.

The effect of male sex hormones on the genitals

In the genitals, male sex hormones have an androgenic effect, that is, they contribute to the development and functioning of these organs and the formation of secondary sexual characteristics during puberty.

Action of male sex hormones on non-sexual organs

In non-sexual organs, androgens have a generalized anabolic effect, that is, they stimulate the synthesis of nucleic acids and protein, retain nitrogen and calcium in the body, and enhance the synthesis of membrane phospholipids.

Central nervous system, hypothalamus, pituitary gland – under the influence of androgens, the formation of typical sexual behavior, instinct and psyche of a man takes place, that is, the behavioral characteristics of the male gender are formed. Androgens affect brain development. If androgen deficiency develops in the fetal period during the critical stages of brain development and differentiation, then this young man or man may develop sexual orientation options in the future. An excess of androgens in the body contributes to aggressiveness.

Bones, cartilages, larynx – androgens contribute to the formation of the characteristic physiological features of the male skeleton, larynx, voice, enhance the deposition of phosphorus-calcium salts in the epiphyseal growth zones. Excessive synthesis of hormones can lead to premature growth of epiphyses and the development of short stature.

Muscles – androgens increase muscle mass and strength, create a characteristic relief of muscles.

Skin – androgens have a stimulating effect on sebaceous glands, increase skin oiliness, increase skin pigmentation (sun tan), increase facial and body hair growth, promote male hair growth. An excess of hormones can lead to baldness.

Adipose tissue – androgens accelerate the breakdown of fat in adipose tissue, inhibit its synthesis.

In the liver and kidneys, androgens dramatically increase protein synthesis, in hematopoietic organs they increase erythropoiesis.

Thyroid hormones

Thyroid hormones – thyroxine (T4) and triiodothyronine (T3) are synthesized in the thyroid gland. The synthesis of these hormones requires iodine, which is actively taken up from the blood by the cells of the follicles of the thyroid gland.

Thyroxine and triiodothyronine are derivatives of the amino acid tyrosine. Thyroxine contains 4 iodine atoms in its molecule, triiodothyronine contains 3 iodine atoms.

The thyroglobulin protein is found in the epithelial cells of thyroid follicles. It is a glycoprotein containing many tyrosine amino acid residues (about 3% of the protein mass). Synthesis of thyroid hormones occurs from tyrosine and iodine atoms precisely in the composition of the thyroglobulin molecule and includes 2 stages. On the apical membranes of follicle cells, tyrosine iodination first occurs with the formation of monoiodotyrosine (MIT) and diiodotyrosine (DIT). The next stage is the condensation of MIT and DIT with the formation of T3 and T4 (fig. 5.6).

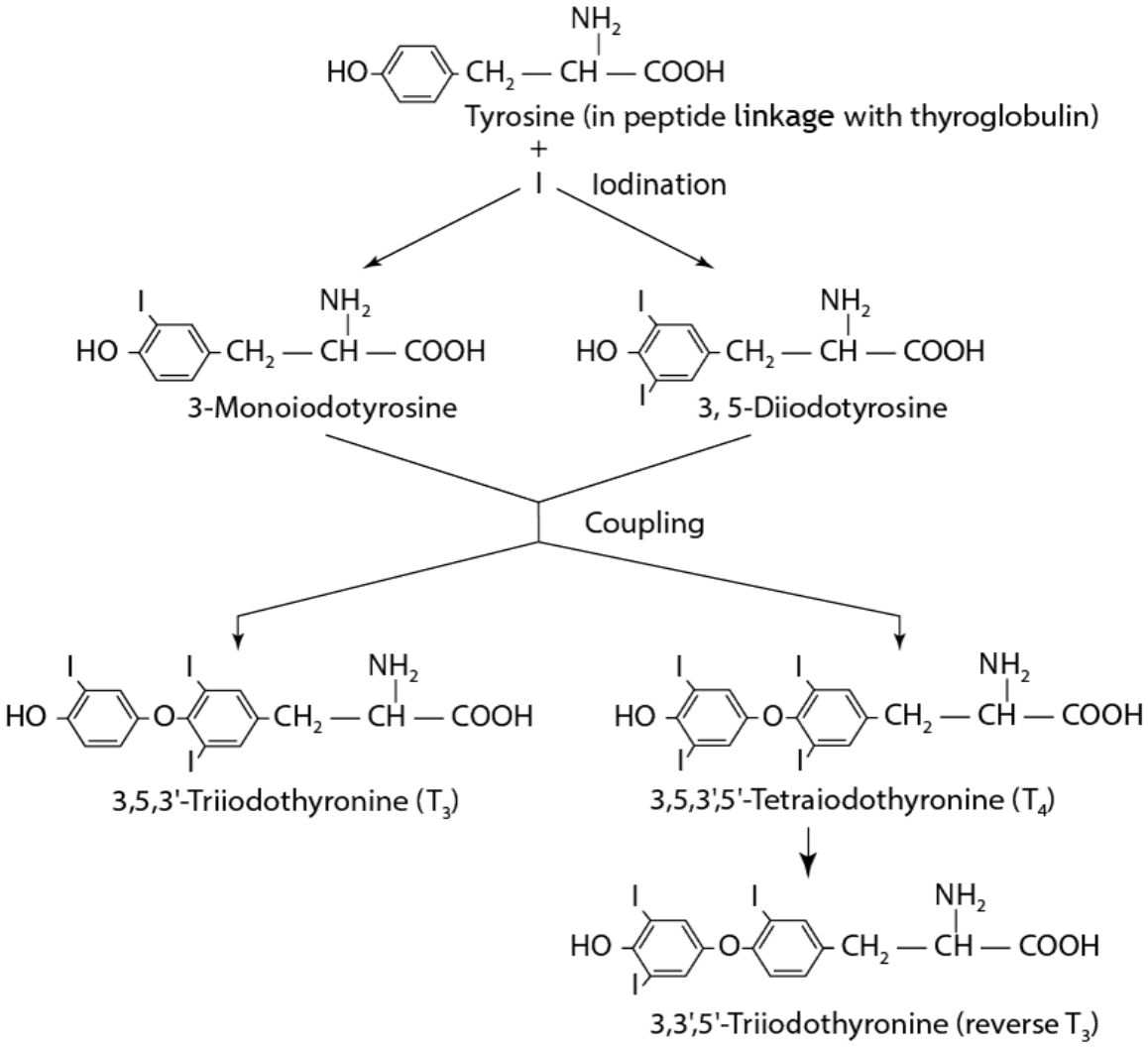


Fig. 5.6. General scheme of synthesis of thyroid hormones

Such an iodinated thyroglobulin molecule is secreted into the lumen of the follicle, into the colloid. When a signal in the form of TSH (thyroid-stimulating hormone) arrives in the thyroid gland, follicle cells capture colloid droplets together with thyroglobulin, lysosome protease enzymes hydrolyze the protein to amino acids and ready T3 and T4 enter the blood.

In the blood, thyroid hormones bind to a carrier protein and are transported in this form to target tissues. The concentration of T4 in the blood is 10 times greater than T3, so T4 is called the main form of thyroid hormones in the blood. But T3 is 4-5 times more active than T4.

Target tissues for thyroid hormones are all tissues except the spleen and testes.

In the target tissues, thyroid hormones are released from the protein and enter the cell. In cells, 90% of T4 loses 1 iodine atom and turns into T3. Thus, the main intracellular form of the hormone is T3.

The effect of thyroid hormones on the body depends on the concentration of these hormones in the blood: in physiological doses, they have an anabolic effect, in large doses – catabolic. Thyroid hormones regulate the basic metabolism, growth and differentiation of tissues, exchange of proteins, carbohydrates, lipids, activity of the central nervous system, etc.

The main effect of physiological concentrations of thyroid hormones is aimed at protein synthesis and energy metabolism.

Effect of T4 on protein synthesis. Through the receptors, the hormone acts on the chromatin of the nucleus, as a result of which the synthesis of nucleic acids (DNA, mRNA) and protein increases. The synthesis of new protein molecules accelerates the growth, division and differentiation of cells, which is very important for a growing body.

Thyroid hormones are absolutely necessary for the structural, biochemical and functional maturation of the brain.

Deficiency of thyroid hormones (hypothyroidism) in the period 1-1.5 years after birth or even before birth leads to a decrease in protein synthesis in the whole body and, in particular, in the brain tissue, the process of differentiation of the cortex

of the large hemispheres and the cerebellum is disturbed, mental and physical retardation develops . Hypothyroidism in children is called cretinism. The earlier the deficiency of thyroid hormones occurs, the more it affects the delay in the development of the central nervous system. Therefore, early diagnosis of hypothyroidism is extremely important in order to timely prescribe the correct treatment and avoid mental retardation.

Effect of T4 on energy metabolism. Thyroid hormones activate energy metabolism, i.e. consumption and synthesis of ATP. Since 2 oppositely directed processes are simultaneously activated, balance is maintained between them. Externally, this is manifested by an increase in the consumption of oxygen by tissues and the generation of heat to maintain a normal body temperature.

The molecular mechanism of action of thyroid hormones on energy metabolism is as follows. Thyroid hormones increase the consumption of ATP for energy-dependent processes, resulting in the formation of ADP. ADP is an activator of the tissue respiration chain (TRC), where ATP is again formed from ADP, which is again spent on energy-dependent processes.

With hyperthyroidism (thyrotoxicosis or Basedow disease) an excess of thyroxine is produced in the body. High concentrations of the hormone act on the mitochondria, which are the “powerhouses” of the cell. In the mitochondria there is TRC, that is, a chain of carriers that oxidizes substrates with the help of oxygen and in which energy is generated. Normally, part of this energy is stored in the form of ATP, and part is used to generate heat to maintain normal body temperature. Synthesis of ATP in TRC is called oxidative phosphorylation. Large concentrations of thyroid hormones separate TRC and oxidative phosphorylation. As a result, TRC works, substrates are oxidized, energy is generated in TRC, but due to disconnection of TRC and oxidative phosphorylation, energy is not stored in the form of ATP, but dissipated in the form of heat. Therefore, one of the characteristic signs of hyperthyroidism is an increase in body temperature. Since the formation of ATP in this disease is reduced, severe weakness is observed, since ATP is necessary for muscle contraction and maintenance of muscle tone. Deficiency of ATP in the body

leads to increased breakdown of proteins, carbohydrates and body fats (catabolic effect of high concentrations of thyroxine), which is accompanied by sudden general weight loss.

Hypofunction of the thyroid gland (hypothyroidism) in adults it is called myxedema. Mucosal swelling of tissues, obesity, hair and teeth loss, apathy, drowsiness, mental inertia, decreased interest and initiative, hypercholesterolemia, fatty degeneration of the liver, speech becomes slow and slurred, facial expressions are unclear, skin is dry, pale and cold, body temperature decreases.

Hypofunction of the thyroid gland (hypothyroidism) in children is called cretinism.

Endemic goiter is a special form of hypothyroidism. It occurs when there is insufficient iodine content in water and food (highland residents often suffer). The thyroid tissue grows compensatory, but in the absence of iodine, this does not lead to an increase in the production of thyroid hormones.

Eicosanoids

The name eicosanoids comes from eicosatetraenoic (arachidonic) acid, from which these compounds are formed. Eicosanoids are called hormone-like substances, as well as local or tissue hormones, because, unlike true hormones, which are formed in some organs (endocrine glands) and act in others (target tissues), eicosanoids act where they are synthesized.

Eicosanoids are formed from arachidonic acid, which is cleaved from membrane phospholipids under the action of phospholipase A2. Arachidonic acid can be transformed in 2 ways: cyclooxygenase, the main enzyme of which is cyclooxygenase (prostaglandin synthetase), and lipoxygenase, with the participation of lipoxygenase. As a result of cyclooxygenase conversion of arachidonic acid, prostaglandins, prostacyclins and thromboxanes are formed. Leukotrienes are synthesized in the lipoxygenase pathway (fig. 5.7). Inhibitors of these enzymes are used to reduce the synthesis of eicosanoids in tissues.

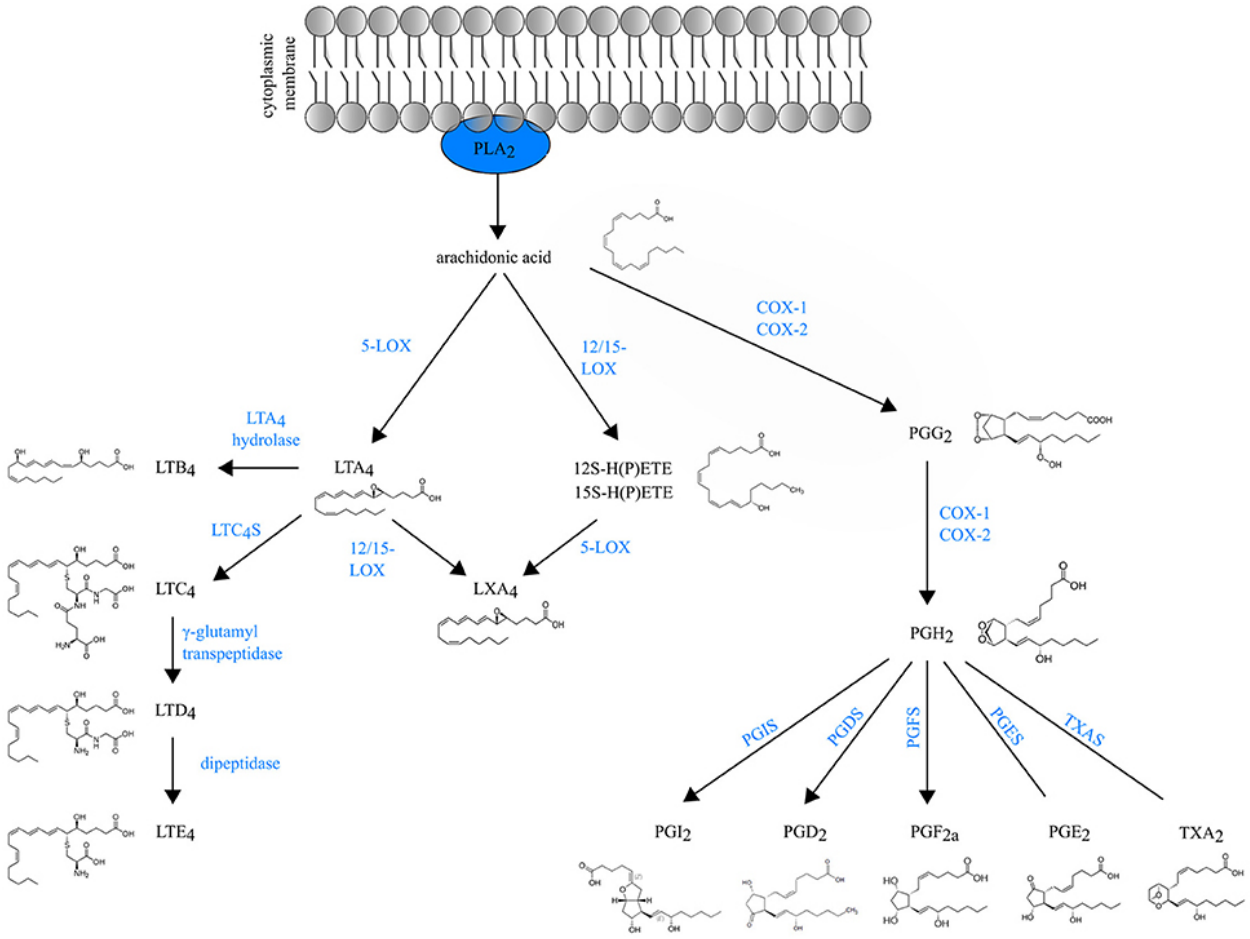


Fig. 5.7. General scheme of synthesis of eicosanoids

Leukotrienes (LT) - participate in inflammation, allergies, immunity, attract leukocytes to the focus of inflammation, narrow the bronchi, increase the secretion of bronchial mucus.

Prostaglandins (PGs) - are mediators with a pronounced physiological effect. They increase the sensitivity of nociceptive receptors (sensitize them) to pain mediators such as histamine and bradykinin. Prostaglandins together with thromboxane and prostacyclin form a subclass of prostanoids, which in turn belong to the class of eicosanoids.

Prostacyclins (PG I_2) - dilate blood vessels, lower blood pressure, prevent aggregation (gluing) of platelets, thereby preventing thrombosis.

Thromboxanes - contribute to platelet aggregation, thereby contributing to thrombosis. Stronger than all compounds, they constrict blood vessels. The

prostacyclin / thromboxan ratio in the vessel wall is of great importance in the development of thrombosis.

Interferons - a group of low-molecular-weight biologically active peptides, proteins, of which more than 20 are currently known. There are four types of interferons (α, β, γ, ω), which differ in origin and some chemical and biological properties. They are combined into two types: type I is alpha-, beta- and omega-interferons, type 2 is gamma-interferon.

α-INTERFERON (leukocyte) produced by lymphocytes, macrophages, and some epithelial cells after induction by various antigens (interferon inducers). Interferon-α inhibits the growth of viruses and other intracellular parasites. It suppresses the connection of the viral RNA with the ribosomes of the cell, which complicates or completely excludes the possibility of reproduction of the virus in the cell, and also inhibits the proliferation of normal fibroblast cells, hematopoietic cells (anti-proliferative, tumoricidal effect).

β-INTERFERON (fibroblastic) - synthesized by fibroblasts. Enhances the expression of HLA-antigens on cells, activates natural killer cells (NK) and phagocytes. The structural affinity of alpha- and beta-interferons, as well as their functional similarity, has been proven. Both types of interferons are induced by viruses and interact with the same cellular receptors. The main effect of α- and β-interferons is antiviral and antitumor. ω (omega) – not studied enough.

γ-INTERFERON (immune) - it is mainly produced by different subclasses of lymphocytes (CD4 cells – T-helpers (Th-1), CD8 cells and NK). Its secretion is observed only after stimulation of cells with antigens or mitogens. It enhances the antiviral and antiproliferative effects of interferons-α and -β. In addition, it is the most important immunoregulator. Gamma-interferon enhances the synthesis of HLA-antigens by cells, which leads to the acceleration of antigen recognition and processing, activates natural killers, T-lymphocytes, macrophages, adhesion of leukocytes and monocytes, phagocytosis, reduces the activity of B-lymphocytes and IgE production, suppresses the production of Th cytokines 2 cells.

2. TASKS FOR INDEPENDENT WORK.

In the table with test tasks, underline the key words, choose the correct answer and justify it:

1.	A patient living in a specific geochemical territory was diagnosed with endemic goiter. What type of post-translational modification of thyroglobulin is disturbed in the patient's body? A. Methylation B. Phosphorylation C. Acetylation D. Glycosylation E. Iodination	
2.	A person has reduced diuresis, hypernatremia, hypokalemia. Hypersecretion of which hormone can cause such changes? A. Adrenaline B. Aldosterone C. Vasopressin D. Parathyroid hormone E. Atrial natriuretic factor	
3.	Using the method of indirect	

	calorimetry, it was established that the subject's basic metabolism was 40% below normal. Violation of the activity of which endocrine gland is the cause? A. Pancreas B. Adrenal glands C. Thymus D. Epiphysis E. Thyroid gland	
4.	A patient complained of constant thirst to the doctor. Hyperglycemia, polyuria and increased content of 17-ketosteroids in urine were detected. Which disease is more likely? A. Addison's disease B. Myxedema C. Glycogenosis of type I D. Steroid diabetes E. Insulin-dependent diabetes	
5.	A patient turned to an endocrinologist with complaints of weight loss of 10 kg in 2 months, palpitations, and constipation. For the hyperfunction of which endocrine gland (which glands)	

	are these complaints most characteristic? A. Thyroid B. Adrenal glands C. Pancreatic D. Parathyroid glands E. Ovaries	
6.	Testosterone and its analogues increase the mass of skeletal muscles, which allows them to be used for the treatment of dystrophies. This action is due to the interaction with which cellular component? A. Membrane receptors B. Ribosomes C. Chromatin D. Nuclear receptors E. Transcription activator proteins	
7.	During the examination of the patient, the doctor suspected Itsenko-Cushing syndrome. Detection of which substance in the patient's blood will confirm the doctor's assumption? A. Adrenaline B. Tocopherol	

	C. Cholesterol D. Retinol E. Cortisol	
8.	In thyrotoxicosis, the synthesis of thyroid hormones T3 and T4 increases, weight loss, tachycardia, and mental agitation develop. How exactly do thyroid hormones affect the energy exchange in cell mitochondria? A. They block substrate phosphorylation B. Separate oxidation and oxidative phosphorylatio C. Activate oxidative phosphorylation D. Activate substrate phosphorylation E. Block the respiratory chain	
9.	A 38-year-old woman complains of increased sweating, palpitations, and an increase in body temperature in the evening. Basic exchange increased by 60%. The doctor diagnosed thyrotoxicosis. What properties lead to increased heat production?	

	A. Reduces deamination of amino acids B. Increases the coupling of oxidation and phosphorylation C. Promotes the accumulation of acetyl-CoA D. Uncouples oxidative phosphorylation E. Reduces β-oxidation of fatty acids	
10.	A patient with a diagnosis of Cushing's disease (hyperproduction of adrenal cortex hormones) has an increased concentration of glucose, ketone bodies, and sodium in his blood. What biochemical mechanism is the leading cause of hyperglycemia? A. Gluconeogenesis B. Glycolysis C. Glycogenolysis D. Glycogenesis E. Aerobic glycolysis	
11.	A 44-year-old woman complains of general weakness, heart pain, significant weight gain. Objectively: moon-shaped face, hirsutism, BP-165/100 mm Hg, height - 164 cm, weight - 103 kg; predominant accumulation of fat on the neck,	

	shoulder girdle, abdomen. What is the main pathogenetic mechanism in women? A. Decreased glucagon secretion B. Increase insulin secretion C. Decreased secretion of thyroid hormones D. Increased secretion of glucocorticoids E. Increased secretion of mineralocorticoids	
12.	A patient with neurodermatitis has been taking prednisolone for a long time. During the examination, he was found to have increased blood sugar. The influence of drugs on which link of carbohydrate metabolism leads to the occurrence of this complication? A. Activation of glycogenolysis B. Increasing the absorption of glucose in the intestine C. Activation of insulin cleavage D. Activation of gluconeogenesis	

	E. Inhibition of glycogen synthesis	
13.	The patient is registered in the endocrinological dispensary for hyperthyroidism. Weight loss, tachycardia, tremors of the fingers were joined by symptoms - headache, fatigue, the appearance of "flies" before the eyes. What mechanism of action of thyroid hormones underlies the development of a hypoenergetic state? A. Specific binding of respiratory enzyme active sites B. Competitive inhibition of respiratory enzymes C. Uncoupling of oxidation and phosphorylation D. Increased synthesis of respiratory enzymes E. Inhibition of synthesis of respiratory enzymes	
14.	The parents of a 10-year-old boy, who has an increase in body hair, growth of a beard and mustache, and a low voice, turned to the doctor. An increase in the secretion of which hormone can be assumed?	

	A. Estrogen B. Progesterone C. Cortisol D. Somatotropin E. Testosterone	
15.	Hyperkalemia and hyponatremia were found in the patient. A decrease in the secretion of which hormone can cause such changes? A. Parathyroid hormone B. Natriuretic C. Aldosterone D. Cortisol E. Vasopressin	
16.	Residents of the territory with a cold climate have an increased content of the hormone in their blood, which has an adaptive thermoregulatory value. What hormone are we talking about? A. Thyroxine B. Glucagon C. Insulin D. Cortisol E. Somatotropin	
17.		

	With a chronic overdose of glucocorticoids, the patient develops hyperkalemia. Name the process of carbohydrate metabolism due to which the concentration of glucose in the blood plasma increases: A. Gluconeogenesis B. Aerobic glycolysis C. Glycogenesis D. Pentose phosphate cycle E. Glycogenolysis	
18.	Aspirin has an anti-inflammatory effect, as it inhibits the activity of cyclooxygenase. At the same time, the level of which biologically active substances will decrease? A. Iodothyronine B. Biogenic amines C. Leukotrienes D. Prostaglandins E. Catecholamines	
19.	During the utilization of arachidonic acid by the cyclooxygenase pathway, biologically active substances are formed. Specify them: A. Insulin-like growth factor	

	B. Somatomedins C. Biogenic amines D. Prostaglandins E. Thyroxine	
20.	Insufficiency of linoleic and linolenic acids in the body leads to skin damage, hair loss, delayed wound healing, thrombocytopenia, and reduced resistance to infectious diseases. Violation of the synthesis of which substances most likely causes these changes? A. Interleukins B. Eicosanoids C. Corticosteroids D. Interferons E. Catecholamines	
21.	Bioregulators of cellular functions of a lipid nature include thromboxanes. The source for the synthesis of these compounds is: A. Phosphatidic acid B. Palmitoleic acid C. Stearic acid D. Palmitic acid E. Arachidonic acid	

3. LITERATURE. See page 320.

LESSON № 6

6. TOPIC: ROLE OF HORMONES IN THE REGULATION OF METABOLIC PROCESSES

1. INFORMATION MATERIAL.

Hormones of the hypothalamus

The hypothalamus vibrates special signals that regulate the hormonal activity of the pituitary gland. Statins reduce, and liberins (releasing factors) increase the synthesis of tropic pituitary hormones.

The hormones of the hypothalamus enter the pituitary gland through the portal veins. Their concentration determines the activity of the pituitary gland, and therefore the function of the peripheral endocrine glands (supraneural, thyroid, ovaries and testicles). At this time, the onset of statin and liberina has been identified:

- gonadoliberins (foliberin and luliberin);
- somatoliberin;
- prolactoliberin;
- thyroliberin;
- melanoliberin;
- corticoliberin;
- somatostatin;
- prolactostatin (dopamine);
- melanostatin.

Pituitary hormones

In the anterior and middle parts of the pituitary gland, tropic hormones are created. The posterior part of the pituitary gland (neurohypophysis) secretes hormones (vasopressin and oxytocin), which are synthesized in the nuclei of the hypothalamus.

Anterior pituitary gland

ACTH - adrenocorticotropic hormone, or corticotropin. Firstly, on the zona fasciculata of the measles of the supra-neural veins, glucocorticoids are created mainly. In addition, ACTH enhances the breakdown of glycogen in the liver and fat in adipose tissue.

TSH - thyroid-stimulating hormone, or thyrotropin. Regulates the development and functioning of the thyroid gland, the synthesis and secretion of thyroid hormones into the blood.

GGT - gonadotropic hormones, or gonadotropins. They reach follicle-stimulating hormone (FSH or folitropin) and luteinizing hormone (LH or lutropin). FSH stimulates the maturation of follicles in the ovaries in women and spermatogenesis in men. LH stimulates the secretion of estrogens and progesterone in women, stimulates the release of the body fluid in the ovaries, and in men it stimulates the secretion of testosterone.

LTG - lactotropic hormone, or prolactin. Stimulates the development of milk ducts and lactation in wives, promotes the formation of father's instincts; in humans it reduces sexual potency.

Lipotropic hormones (lipotropins)- perform fat-mobilizing action (increase fat breakdown).

STH - somatotropic hormone, or somatotropin, which is also called “growth hormone”. The particularity of the hormone is highly dependent on species specificity. This means that STH creatures are not relevant to people.

Stimulators of somatotropic hormone secretion:

1. sleep, especially in the first years after falling asleep (since a child doesn’t sleep enough, his growth is stunted);

2. cold (in general, northerners are better than natives);

3. stress (if a child is protected from normal everyday stress, she will grow in height);

4. physical demands (in general, athletes are more likely to lack regular physical demands).

Target tissues for STH are all tissues in the body.

Effect of STH on the body

1. Anabolic. In the cells of STH, it increases the synthesis of DNA, RNA and protein, stimulates the growth of bones (osteogenesis), cartilage (chondrogenesis) and soft tissues, regulates the processes of growth and development of the skeleton and the whole body, leads to an increase in body size. The cartilaginous tissue of the epiphyses is most sensitive to the action of STH, due to this, tubular bones grow in length.

2. Diabetogenic. In the liver, STH activates gluconeogenesis (through stimulation of glucagon secretion). In muscles and adipose tissue, THG reduces the permeability of membranes for the transport of amino acids into the cell. In excess of THG, the concentration of glucose in the blood increases and insulin resistance of peripheral tissues develops, i.e. somatotropic diabetes.

3. Lipolytic. In children during the period of intensive growth, there are no fat deposits, since in adipose tissue, STH enhances the breakdown of fat into fatty acids. Fatty acids enter the blood and are utilized in the tissues. In excess STH the concentration of fatty acids in the blood increases significantly and they are intensively used by the liver in 2 directions:

• on fat synthesis (therefore in excess STH fatty degeneration of the liver develops);

• on beta-oxidationя, resulting in the formation of acetyl-CoA, which is used for the formation of ketone bodies (therefore in excess STH the concentration of ketone bodies in the blood increases).

Pathology

In case of lack of production STH (pituitary dwarfism, or dwarfism) there is proportional underdevelopment of the whole body, short stature, but, unlike cretinism, there are no signs of skeletal deformation and mental retardation.

Hypersecretion STH occurs with tumors of the adenohypophysis. If such a condition develops in childhood, before the ossification of the skeleton is completed, gigantism is observed, the signs of which are excessive growth of the skeleton and disproportionately long limbs. If hypersecretion STH occurs in adults, that is, after the completion of skeletal growth, acromegaly is observed. This disease is characterized by disproportionately intense growth of individual parts of the skeleton (hands, feet, chin, browbones, nose), growth of soft tissues of the face (lips, nose, tongue), as well as an increase in endocrine glands, which may be accompanied by their hyperfunction.

The middle lobe of the pituitary gland

MSG – melanocyte-stimulating hormone, or melanotropin. Increases the number of pigment cells (melanocytes) and stimulates the production of melanin pigment in the skin, iris and retina.

The posterior lobe of the pituitary gland

Oxytocin and vasopressin are only conditionally classified as hormones of the posterior lobe of the pituitary gland, since they are synthesized in special neurons of the hypothalamus (in the supraoptic and paraventricular nuclei). These hormones enter the posterior part of the pituitary gland through the processes of neurons, where they are deposited and from where they are directly released into the blood.

Oxytocin. Peptide hormone consists of 9 amino acid residues. The synthesis of this hormone is carried out in the hypothalamus with subsequent secretion into the posterior lobe of the neurohypophysis with the carrier protein - neurophysin. Oxytocin is a stimulator of the smooth muscles of the uterus during childbirth, as well as oxytocin is a stimulator of lactation. The signal for the release of oxytocin is mechanical irritation of the papillae of the mammary gland, where the receptors for oxytocin are located.

vasopressin, or antidiuretic hormone. Hormone of peptide nature, consists of 9 amino acid residues . Most of the hormone is synthesized by large-cell neurons of the supraoptic nucleus of the hypothalamus, the axons of which are directed to the posterior lobe of the pituitary gland ("neurohypophysis") and form synapse-like

contacts with blood vessels. Vasopressin, synthesized in the bodies of neurons, is transported by axonal transport to the ends of axons and accumulates in presynaptic vesicles. It is secreted into the blood when the neuron is excited, causes a contraction of vascular smooth muscle, which leads to narrowing of blood vessels and an increase in blood pressure (V1 receptors). In addition, vasopressin exerts a powerful antidiuretic effect - it stimulates the reverse absorption (reabsorption) of water in the kidneys and reduces the volume of excreted urine (V2 receptors). With atrophy of the posterior lobe, the pituitary gland develops *diabetes insipidus* - a disease in which an extremely large amount of fluid is excreted in the urine (10-20 liters per day).

Pancreatic hormones

Insulin – a hormone of a protein nature, synthesized in the β-cells of the islets of Langerhans of the pancreas, stored in secretory granules in connection with zinc and released into the blood in response to an increase in the concentration of glucose in the blood.

According to sensitivity to insulin, all tissues can be divided into 3 groups:

1. The main target tissues or completely insulin-dependent tissues. They have maximum sensitivity to insulin. Fat tissue and muscles belong to this group. Glucose does not penetrate into these tissues and is not utilized in them during the absence of insulin.

2. Absolutely insulin-independent tissues. These include the brain, red blood cells, the mucous membrane (epithelium) of the small intestine, the medulla of the kidneys, and the testicles. Glucose easily penetrates the cells of these tissues even in the absence of insulin and is the only energy substrate for them. Moreover, the brain consumes 50% of all glucose in the body, the kidneys and erythrocytes - another 20%. Thus, it is extremely important for the body that the main metabolic fund of glucose and vital functions are independent of insulin.

3. Relatively insulin-dependent tissues. These are all other fabrics. In terms of sensitivity to insulin, they occupy an intermediate position between the tissues of the 1st and 2nd groups.

Effect of insulin on intracellular metabolism

1. Insulin is the only hormone that lowers the concentration of glucose in the blood. This effect of the hormone is due to the following mechanisms:

• insulin increases the permeability of membranes for the transport of glucose from the blood into the cells;

• insulin activates the use of glucose through glycolysis (oxidative breakdown of glucose) and glycogen synthesis;

• insulin inhibits the breakdown of glycogen (glycogenolysis) and gluconeogenesis (the process of forming glucose from amino acids).

2. Insulin is a universal anabolic hormone. It enhances the processes of synthesis of nucleic acids, proteins, fats, glycogen and inhibits their decay. In addition, the anabolism of insulin is manifested in the fact that it activates processes (glycolysis, the tricarboxylic acid cycle) that provide energy for synthesis.

Glucagon — hormone of the α-cells of the islets of Langerhans of the pancreas. Chemically, glucagon is a peptide hormone. Glucagon molecule consists of 29 amino acids. Especially a lot of glucagon is synthesized during fasting, that is, glucagon is the main hormone that maintains the level of glucose in the blood during this state.

Main target tissues for glucagon: liver, adipose tissue, renal cortex, cardiac (but not skeletal) muscle.

In the liver, the hormone stimulates the breakdown of glycogen into glucose during the first day of fasting. But since glycogen reserves in the liver completely disappear after a day, starting from the second day of fasting, glucagon activates gluconeogenesis in the liver, that is, the synthesis of glucose from amino acids formed during protein breakdown. Thus, thanks to the two mentioned mechanisms (increased breakdown of glycogen and activation of gluconeogenesis in the liver), glucagon maintains the concentration of glucose in the blood during fasting.

Also, in the liver, glucagon inhibits glycolysis, reduces the synthesis of glycogen and fatty acids, but activates the synthesis of ketone bodies.

In adipose tissue, glucagon increases the breakdown of fat and inhibits its synthesis.

In the cortical substance of the kidneys, glucagon activates gluconeogenesis.

In all target tissues, glucagon increases protein breakdown and decreases protein synthesis.

2. TASKS FOR INDEPENDENT WORK.

In the table with test tasks, underline the key words, choose the correct answer and justify it:

1	For the purpose of analgesia, substances that imitate the effects of morphine, but are produced in the central nervous system, can be used. Specify them. A. Somatoliberin B. Calcitonin C. Vasopressin D. Oxytocin E. β-endorphin	
2	In a patient with a chronic inflammatory process of the skin and subcutaneous tissue, a predominance of proliferation processes was found. Deficiency of which hormone can lead to this? A. Cortisone B. Insulin C. Thyroxine D. STG	

	E. Aldosterone	
3	The patient took glucocorticoids for a long time. After abrupt discontinuation of the drug, he complains of myalgia, increased fatigue, emotional instability, headache, insomnia, loss of appetite, nausea. Glucocorticoid withdrawal syndrome developed. What drugs are prescribed to correct this condition? A. Mineralocorticoids B. Glucocorticoids S. AKTG D. Adrenaline E. Corticosteroids	
4	An elderly patient was observed to have increased and thickened fingers, hands, feet, nose and lower jaw. These disorders are associated with an increase in the release of which hormone? A. Parathyroid hormone B. Insulin C. Adrenocorticotropin D. Thyrotropin E. Somatotropin	
5	A 55-year-old patient is being	

	examined by an endocrinologist regarding a violation of the endocrine function of the pancreas, which is manifested by a decrease in the amount of the glucagon hormone in the blood. The function of which cells of this gland is disturbed in this case? A. δ1 cells of the islets of Langerhans B. δ-cells of the islets of Langerhans C. α-cells of the islets of Langerhans D. PP cells of the islets of Langerhans E. β-cells of the islets of Langerhans	
6	A very tall patient with long thick fingers, a large lower jaw and a drooping lower lip came to the doctor for an appointment. Increased secretion of which hormone of which gland can be suspected? A. Thyroid hormones B. Antidiuretic hormone of the posterior lobe of the pituitary gland C. Somatotropic hormone of the	

	anterior lobe of the pituitary gland D. Gonadotropic hormone of the anterior lobe of the pituitary gland E. Adrenal hormones from the group of glucocorticoids	
7	Taking oral contraceptives containing sex hormones inhibits the secretion of pituitary hormones. The secretion of which of the hormones listed below is inhibited when taking oral contraceptives containing sex hormones? A. Somatotropic B. Oxytocin S. Follicle stimulating D. Vasopressin E. Thyreotropic	
8	In a patient who had been taking glucocorticoids for a long time, as a result of withdrawal of the drug, there was an exacerbation of the existing disease, a decrease in blood pressure, and weakness. How can these phenomena be explained? A. Sensitization B. Development of adrenal insufficiency C. Hyperproduction of ACTH D. Cumulation	

	E. Addiction to the drug	
9	A 50-year-old patient complains of thirst, drinks a lot of water, and has pronounced polyuria. Blood glucose is 4.8 mmol/l, there is no glucose or acetone bodies in the urine, the urine is colorless, the specific gravity is 1.002-1.004. What is the cause of polyuria? A. Aldosteronism B. Insulin deficiency C. Insufficiency of vasopressin D. Hypothyroidism E. Thyrotoxicosis	
10	A mother, whose son grew 18 cm during the summer, turned to the doctor. During the examination of the 12-year-old boy: height - 180 cm, weight - 68 kg. It can be connected with the hyperfunction of which endocrine gland? A. Adrenal glands B. Pancreatic C. Thyroid D. Epiphysis E. Hypophysis	
11	A person, as prescribed by a doctor, took a drug from the group of glucocorticoid hormones for a long	

	time. The secretion of which of the following hormones will be inhibited as a result? A. Thyrotropic V. Kortikotropic C. Sexual D. Somatotropic E. Mineralocorticoids	
12	Due to the loss of 1.5 liters of blood, a person's diuresis decreased sharply. Increased secretion of which hormone caused a change in diuresis? A. Parathyroid hormone B. Corticotropin C. Cortisol D. Vasopressin E. Natriuretic	
13	A pregnant woman with weak labor was admitted to the maternity ward. Prescribe a hormonal agent to enhance labor activity: A. Hydrocortisone B. ACTH C. Oxytocin D. Methandrostenolone E. Progesterone	
14	The patient has a reduced synthesis of vasopressin, which leads to	

	polyuria and, as a result, severe dehydration of the body. What is the mechanism of development of polyuria? A. Increasing the rate of glomerular filtration B. Decreased tubular reabsorption of Na ions C. Decreased tubular reabsorption of protein D. Reduction of glucose reabsorption E. Decreased tubular reabsorption of water	
15	A 32-year-old woman turned to the doctor with complaints about the lack of lactation after the birth of a child. This disorder can be explained by the deficiency of which hormone? A. Glucagon B. Prolactin C. Thyrocalcitonin D. Somatotropin E. Vasopressin	
16	Products of hydrolysis and modification of some proteins are biologically active substances-hormones. Lipotropin,	

	corticotropin, melanotropin and endorphins are formed from which of the following proteins in the pituitary gland? A. Thyroglobulin B. Neurostromin C. Neuroglobulin D. Proopiomelanocortinin (POMK) E. Neuroalbumin	
17	A 40-year-old patient complains of a strong heartbeat, sweating, nausea, visual disturbances, hand tremors, and increased blood pressure. From the anamnesis: a pheochromocytoma was diagnosed 2 years ago. Hyperproduction of which hormones causes this pathology? A. Thyroid hormones B. Catecholamines C. Glucocorticoids D. ACTH E. Aldosterone	
18	After parenteral administration of the hormone, the patient's blood pressure increased, and the level of glucose and lipids in the blood increased. What hormone was injected?	

	A. Progesterone B. Insulin C. Glucagon D. Folliculin E. Adrenaline	
19	The secretion of which pituitary hormones is inhibited after taking oral contraceptives containing sex hormones? A. Gonadotropic B. Somatotropin C. Thyrotropic D. Oxytocin E. Vasopressin	
20	Animals were intravenously injected with a solution of sodium chloride, which caused a decrease in the reabsorption of sodium ions in the kidney tubules. How and which hormone does the secretion change? A. Reduction of the natriuretic factor B. Increase in aldosterone C. Reduction of aldosterone D. Increase in glucagon E. Reduction of vasopressin	
21	After suffering sepsis, the 27-year-old patient developed a bronze skin	

	color, characteristic of Addison's disease. The mechanism of hyperpigmentation consists in increasing the secretion of such a hormone: A. Melanocyte-stimulating B. Beta-lipotropic C. Thyrotropic D. Gonadotropic E. Somatotropic	
22	In a 28-year-old patient, prolonged vomiting led to dehydration. The increased secretion of which hormone primarily contributes to water retention in the body? A. Aldosterone B. Thyroxine C. Somatostatin D. Vasopressin E. Calcitonin	
23	As a result of a household injury, the patient suffered significant blood loss, which was accompanied by a drop in blood pressure. The action of which hormones ensures the rapid recovery of blood pressure caused by blood loss? A. Oxytocin	

	B. Cortisol C. Sexual D. Aldosterone E. Adrenaline, vasopressin	
24	A 26-year-old woman was admitted to the maternity ward at 40 weeks of pregnancy. The cervix is open, but there are no uterine contractions. The doctor gave a remedy of a hormonal nature to increase labor activity. Name this tool: A. Testosterone B. Estrone C. Hydrocortisone D. Oxytocin E. ACTH	

3. LITERATURE. See page 320.

LESSON №7

7. TOPIC: Intermediate control on basic topics 6, 7. Control work #2.

1. THE PURPOSE OF THE LESSON:

To determine the level of students' assimilation of the basic principles of molecular biology and biochemistry of intercellular communications.

3. LIST OF CONTROL QUESTIONS:

1. Chromoproteins, classification, biological role.
2. hemoglobin: structure, properties, biological role. Abnormal forms of hemoglobin in hemoglobinoses (hemoglobinopathy, thalassemia). Hemoglobin derivatives. Types of hemoglobin.
3. Stages of hemoglobin synthesis, regulation of the process.
4. Porphyrins: structure, scheme of biosynthesis reactions of protoporphyrin IX and heme. Regulation of porphyrin synthesis.
5. Hereditary disorders of biosynthesis of porphyrins. Types of porphyria.
6. Hemoglobin catabolism (scheme). Formation of bile pigments. The role of the liver in the exchange of bile pigments.
7. Violation of the metabolism of bile pigments.
8. Types of jaundice: pathobiochemistry and diagnostics.
9. Nucleoproteins: structure, biological functions, classification.
10. Molecular organization of nuclear chromatin of eukaryotes: nucleosomes, histones and non-histone proteins.
11. Nucleic acids. Comparative characteristics of DNA and different types of RNA: structural features (primary, secondary, tertiary structures, Watson-Crick model, Chargaff rules), localization, functions.
12. Nitrogenous bases, nucleosides and nucleotides - structure and biological role.

13. Free nucleotides and their derivatives (ATP, GTP, UTP, CTP, NAD, NADP, FAD, FMN, c-AMP, c-GMP) - structure and functions.

14. Biosynthesis of purine nucleotides: scheme of reactions, regulation of the process.

15. Biosynthesis of pyrimidine nucleotides: scheme of reactions, regulation of the process.

16. Biosynthesis of deoxyribonucleotides: scheme of reactions, regulation of the process. Formation of dTMF, inhibitors of its biosynthesis.

17. Catabolism of purine nucleotides. Disorders of purine metabolism. Gout.

18. Catabolism of pyrimidine nucleotides. End products of their decay. Catabolism of purine nucleotides. Disorders of purine metabolism. Gout.

19. Catabolism of pyrimidine nucleotides. End products of their decay.

20. Nucleoproteins: structure, biological functions, classification

21. Molecular organization of nuclear chromatin of eukaryotes: nucleosomes, histones and non-histone proteins.

22. Nucleic acids. Comparative characteristics of DNA and different types of RNA: structural features (primary, secondary, tertiary structures, Watson-Crick model, Chargaff rules), localization, functions.

23. Molecular mechanisms of DNA replication. Types of replication. Sequence of stages and enzymes of DNA replication in proto- and eukaryotes.

24. General characteristics and types of mutations. Mechanisms of action of mutagens. Mechanisms of DNA repair. The concept of molecular diseases, hereditary diseases and enzymopathies. Genetic engineering.

25. Modern ideas about the mechanism of transcription. RNA polymerases of pro- and eukaryotes. Transcription signals. Post-transcriptional processing of mRNA in eukaryotes.

26. Biochemical composition, structure and functions of biological membranes. Liquid-mosaic model and asymmetry of membranes. The role of lipids in their composition.

27. Genetic code and its properties.

28. Ribosomal protein-synthesizing system of the cell.

29. The role of m-RNA, t-RNA and r-RNA in protein biosynthesis.

30. Mechanism of translation and its stages: initiation, elongation and termination. Initiation, elongation and termination factors in pro- and eukaryotes.

31. Activation of amino acids: mechanism, role of aminoacyl-tRNA synthetases.

32. Energy supply of protein synthesis. Post-translational processing. Broadcast regulation.

33. Modern ideas about the intracellular regulation of prokaryotic gene expression (the operon hypothesis of F Jacob and J. Mono). The concept of the mechanisms of gene induction and repression.

34. Antibiotics are inhibitors of various stages of protein biosynthesis: inhibitors of initiation (stretomycin, rifamycin), elongation (erythromycin, chloramphenicol, tetracyclines, cyclohexamide, puromycin) and termination (lincomycin, amicetin, erythromycin, chloramphenicol, streptomycin).

35. Hormones: general characteristics, structure, properties, modern research methods. The role of hormones and other bioregulators in ensuring the intercellular integration of human body functions.

36. Classification of hormones. Correlation of the structure and mechanism of action of hormones.

37. The concept of target organs and cells of hormones. Types of receptors: features of the structure and localization in the cell. Membrane (ionotropic, metabotropic) and cytosolic receptors.

38. Relationship and regulation of hormone secretion. Principles of forward and reverse feedback, long and short feedback chains.

39. Biochemical systems of intracellular transmission of hormonal signals: G-proteins, secondary mediators (cAMP, calcium/calmodulin, IF3, DAG, phospholipase C), protein kinases.

40. Membrane mechanism of action of protein-peptide hormones.

41. Membrane-intracellular mechanism of action of hormones. Functions of the components of the hormonal signal transmission system in the cell.

42. Cytosolic mechanism of action of lipophilic (steroid and thyroid) hormones.

43. Hormones of the hypothalamus - liberins and statins: features of the structure, secretion and effect on the pituitary gland.

44. Neuropeptides (vasopressin, oxytocin): structure, synthesis and secretion, functions. Diabetes insipidus.

45. Hormones of the anterior lobe of the pituitary gland (somatotropin, thyrotropin, pro-lactin): chemical nature, regulation of secretion, influence on metabolism and secretion disorders. Hormones - products of post-translational processing of proopiomelanocortin (corticotropin, melanotropin, lipotropins, endorphins): chemical nature and biochemical effects.

46. Vasopressin and oxytocin: chemical nature, localization of synthesis and secretion, biochemical functions. Diabetes insipidus.

47. Pancreatic hormones (insulin and glucagon): chemical nature, features of biosynthesis, regulation of secretion and influence on metabolism. Growth-stimulating effects of insulin.

48. Eicosanoids (prostaglandins, thromboxanes, prostacyclins, leukotrienes): ways of formation, biochemical effects. The use of medicinal drugs in the regulation of eicosanoid metabolism.

49. Mediators and hormones of the immune system (cytokines, interferons): chemical nature, synthesis, biochemical effects

LESSON №8

8. TOPIC: THE ROLE OF WATER-SOLUBLE VITAMINS IN METABOLISM. VITAMIN - LIKE SUBSTANCES. THE ROLE OF FAT-SOLUBLE VITAMINS IN METABOLISM. ANTIVITAMINS

1. INFORMATION MATERIAL.

Vitamins (from Latin vita — life) called low-molecular bioregulators, which are necessary in small quantities for normal human activity and must come with food, since the body cannot meet its need for them through biosynthesis. Vitamins do not include ordinary food products that provide energy and protein needs of the body, as well as inorganic salts and trace elements necessary for life. The biosynthesis of a number of vitamins can still take place in the body, but under the influence of external factors, for example, UV radiation (vitamins of group D) or from certain precursors (provitamins) that come with food (for example, vitamin A is synthesized from carotenes). Most vitamins are coenzymes or their precursors and participate in numerous enzymatic reactionsx.

Features of absorption of water-soluble vitamins in the gastrointestinal tract

Vitamin B12 (cyanocobalamin)	It loses its activity in products with a high content of vitamin C. Microorganisms in the human rectum are able to synthesize cobalamin, but in this part of the gastrointestinal tract it is no longer adsorbed and has no functional value. B12 is released from food at low pH values of the environment, that is, in the stomach, where it binds to glycoprotein R (from the English rapid - fast movement during electrophoresis). R-glycoprotein (gastromucoprotein) is contained in many fluids secreted by various parts of the gastrointestinal tract, such as saliva, bile, pancreatic juice, etc. For the absorption of B12, the presence of another factor secreted in the stomach is

	necessary - intrinsic factor (IF) Castle's factor. The B12/R complex together with IF leave the stomach and enter the duodenum. In this part of the gastrointestinal tract, under the action of pancreatic proteases and in the presence of bicarbonates (neutral pH), the B12/R complex is hydrolyzed and the vitamin released, which immediately binds to IF and is transported to the distal part of the intestine. There, the B12/IF complex binds to specific receptors located on intestinal enterocytes and is transported by an ATP-dependent transporter into the blood, where it binds to a protein known as transcobalamin. Free B12 does not bind to these receptors and thus cannot be absorbed into the blood.
Vitamin B1 (thiamine)	It is absorbed in the proximal (middle) part of the small intestine. Having a high concentration, it can enter the blood by passive diffusion, at low concentrations it is absorbed with the participation of a Na-ATP-dependent membrane transporter. Such ions as Ca^{2+} and Mg^{2+} significantly reduce the solubility of thiamine in an aqueous solution, as a result, reduce the absorption capacity.
Vitamin B2 (riboflavin)	It is released from food proteins with the help of proteases and hydrochloric acid in the stomach. It is absorbed in the proximal part of the small intestine with the participation of Na-ATP-dependent transporter. Reduction in the efficiency of the absorption process occurs in the presence of ions Cu^{2+}, Zn^{2+} and Fe^{2+} .
Vitamin B3 (niacin, nicotinic acid)	It is adsorbed in the small intestine as nicotinic acid or nicotinamide. At low concentrations, it is transported by means of Na-dependent diffusion. At high concentrations - by passive diffusion. In the basal cells of enterocytes,

	nicotinic acid is converted to NAD and then hydrolyzed to nicotinamide. It is transported in the blood plasma in the form of free nicotinamide or a nicotinic acid/blood protein complex.
Vitamin B6 (pyridoxine)	Absorption of pyridoxine is maximal already in the duodenum, remains high in the proximal part and absent in the distal part. Thus, the absorption of pyridoxine decreases as the chyme moves through the small intestine.
Vitamin C (ascorbic acid)	In the gastrointestinal tract, it is adsorbed in the distal part of the small intestine with the participation of an ATP-dependent transporter. With an increase in the concentration of the vitamin, its absorption also increases due to the inclusion of the mechanism of passive diffusion. In addition, the absorption of vitamin C is directly proportional to the rate of its release from food. Taking C is undesirable to combine with vitamin B12, because in a dosage higher than 500 mg, it causes the destruction of vitamin B12 and blocks its absorption.

The causes of hypo- and vitamin deficiency in humans and animals are usually divided into exo- and endogenous. First of all, insufficient supply of vitamins or their complete absence in food is the first. Accordingly, insufficient and substandard nutrition is most often the cause of the development of exogenous vitamin deficiency. Endogenous reasons, which are obviously more significant, are:

a) increased need for vitamins in some physiological and pathological conditions (pregnancy, lactation, thyrotoxicosis, cachexic diseases, etc.);

b) increased breakdown of vitamins in the intestines due to the development of microbiota in it;

c) violation of the process of absorption of vitamins as a result of damage to the secretory and motor functions of the intestines in diseases of the digestive tract, when a relative deficiency of vitamins develops even with a full diet;

d) diseases of the liver and pancreas that cause obstruction of the common bile duct and are accompanied by impaired absorption of fats, their breakdown products - fatty acids and actually fat-soluble vitamins; in these cases, secondary (endogenous) vitamin deficiencies also develop.

Vitamin B1 (thiamine, aneurin, aneurin). The form of vitamin B1 that works in the body is its diphosphate (thiamine pyrophosphate), which is also called cocarboxylase; in medicine, in addition, thiamine monophosphate and a large number of its derivatives are used, which are transformed into cocarboxylase in the process of metabolism.

Cocarboxylase is a prosthetic group of a number of enzymes, the biochemical function of which is to decarboxylate PVC and split C—C bonds of other α-keto acids and α-ketoalcohols, as a result of which the biosynthesis of acyl derivatives of coenzyme A becomes possible.

Excessive accumulation of α-keto acids, especially PVC, which is formed during the enzymatic breakdown of carbohydrates, is extremely harmful to the body. Lack of vitamin B1 in food causes the disease beriberi, which is especially widespread in Southeast Asia.

A healthy person's need for thiamine is small and amounts to only 1.5-2 mg/day, but it is often not supplied through food. With many cardiovascular and nervous diseases, the use of large amounts of thiamine or cocarboxylase becomes necessary. In patients with alcoholism, hypovitaminosis B1 is a consequence of nutritional disorders and decreased appetite. At the same time, the aerobic breakdown of glucose is disturbed.

Vitamin B2 or riboflavin, is a D-ribityl derivative of the isoalloxazine heterocyclic system; such derivatives have a common name - flavins. More than 20 biologically active substances of this type have already been isolated from natural

sources. Flavin coenzymes are of great biochemical importance: flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD).

Due to the redox transformation of the flavin ring, flavin coenzymes carry out redox reactions as part of many important enzyme systems: oxidases (in particular, oxidases of D- and L-amino acids, monoamine oxidases, which regulate the level of catecholamines in the blood) and FAD-dependent dehydrogenases (systems with the participation of nicotinamide adenine dinucleotide and ubiquinone).

The main sources of riboflavin and its coenzyme forms are milk, vegetables, liver, kidneys and yeast; additionally, it enters the body also due to the activity of the intestinal microbiota. In case of vitamin deficiency, first of all, skin diseases (seborrhea, psoriasis) usually develop, cracks appear in the corners of the mouth (cheilosis), inflammation of the mucous membrane of the oral cavity, damage to the retina and cornea of the eye, and then a number of diseases of the hematopoietic system and gastrointestinal tract appear , muscle weakness and growth arrest of young organisms. The need for riboflavin is 2-4 mg/day, but therapeutic doses can reach 5-19 mg/day.

Vitamin B5 was found in yeast and named pantothenic acid; it is also often called the "universal vitamin". Vitamin B5 is part of an important cofactor of biological acylation enzymes — coenzyme A, in which its primary hydroxyl is phosphorylated by triphosphoadenosine, and its carboxyl is amidated by 3-mercaptoethylamine.

With a lack of pantothenic acid in the diet, animals develop dermatitis, hair loss and a number of other complications, including changes in the myelin sheaths of the spinal cord. Vitamin B5 deficiency is rare in humans, as Escherichia coli synthesizes a sufficient amount of pantothenic acid, which is then absorbed from the intestines. The daily requirement of a person is about 10 mg. It is mostly found in yeast, peas, milk, eggs, liver, heart and kidneys. Pantothenic acid in terms of biological activity in animals is completely replaced by D-pantothenol and pantothein.

Vitamin B3, another name of which is vitamin PP (from English Pellagra preventing factor is an anti-pellagra factor) or niacin, chemically represents two substances with the same vitamin activity: nicotinic acid (niacin) and nicotinamide (niacinamide). Vitamin B3 plays a biochemical role in the form of coenzymes: nicotinamide adenine dinucleotide (NAD) and nicotinamide dinucleotide phosphate (NADP).

These coenzymes are part of a large group of oxidoreductases (dehydrogenases), participating in almost 150 different biochemical reactions of dehydrogenation, oxidation, N-alkylation, isomerization, reduction of nitrate to nitrite and further to ammonia, photosynthesis, respiration, energy exchange, anaerobic breakdown of carbohydrates etc. In the process of redox reactions, NAD+ and NADP+ react as part of enzymes with organic substrates, stereospecifically (most often from below the pyridine ring) taking a hydride ion from them and forming NADH and NADPH; the reverse reaction also occurs stereospecifically. Healthy people are not very sensitive to insufficient or even absent nicotinic acid in food. The fact is that the provitamin of niacin is tryptophan. The lack of this essential amino acid in corn or sorghum (where they became staple foods) was the cause of pellagra. The most characteristic signs of pellagra are symmetrical lesions of open areas of the skin (dermatitis), gastrointestinal tract (diarrhea) and impaired nervous activity (dementia).

Vitamin B6 (Adermin) can exist in three different chemical forms: pyridoxine, pyridoxal and pyridoxamine. A significant proportion of vitamin B6 enters the human body due to the activity of intestinal microbiota. Biochemical reactions catalyzed by pyridoxal enzymes include reactions of peramination and decarboxylation of amino acids. Pyridoxal and pyridoxamine phosphates are part of more than 50 enzymes involved in the processes of amino acid synthesis and metabolism, as well as in the phosphorylation of carbohydrates, the metabolism of fatty acids, membrane unsaturated lipids.

When it is insufficient, animals usually experience: a specific skin disease ("symmetrical" dermatitis), convulsions, anemia, and growth retardation of young

individuals. Vitamin B6 deficiency usually does not occur in adults, but taking large amounts of the antituberculosis drug isoniazid, which can chemically bind pyridoxal, can cause nausea, seborrheic dermatitis, cheilosis, and other pellagra-like diseases. Convulsions associated with a deficiency of γ-aminobutyric acid (GABA) and pyridoxine, necessary for the normal functioning of one of the forms of glutamate decarboxylase, are observed in children on inadequate artificial feeding. Pyridoxine, pyridoxal-5'-phosphate and some of their derivatives are widely used in medicine for the treatment of skin and neurological diseases, as well as in chronic hepatitis, in gynecology, hematology, phthisiology and sports medicine.

Vitamin B9 (vitamin Bs). Folic acid performs its biochemical functions in the form of a coenzyme - tetrahydrofolic, folinic acid, which is formed from the vitamin as a result of reduction by folate reductase with the participation of NADPH. Folinic acid in the form of appropriate N5- and/or N10-alkylated derivatives is able to transfer one-carbon radicals as part of enzymes: formyl, oxymethyl, methyl, methylene, methine and formimine (CH=NH), thereby participating in the synthesis of amino acids (for example, serine or methionine), purine and pyrimidine bases, NC, choline, etc.

In medicine, folic acid is used to fight diseases of the hematopoietic system, especially in malignant anemia and radiation sickness, because it participates in the processes of hematopoiesis (it is necessary for the regulation of erythropoiesis, thrombocytopoiesis, and especially leukopoiesis). On the contrary, in the treatment of some other malignant tumors (leukemias, leukemias, trophoblastic formations), which require a large amount of NC for their development, antagonists of folic acid (antivitamin Bs) are often used - aminopterin and methotrexate (ametopterin), which can strongly reduce the activity of folate reductase and thereby suppressing the biosynthesis of nucleic bases and mitosis. Folic acid is widely distributed in nature in plant and animal tissues and, in addition, is produced in large quantities by intestinal microbiota. Unlike humans, many microorganisms cannot use exogenous folic acid and are forced to synthesize it themselves. Therefore, for them, paraaminobenzoic acid is a necessary factor for growth and development, and

paraaminobenzenesulfamide (white streptocide) and its derivatives (sulfanilamide drugs) can act as its antivitamins.

Vitamin B12 (anti-anemic vitamin, oxycobalamin, cyanocobalamin, hematopoietic factor). The history of the discovery of this vitamin is closely related to the search for the causes of pernicious anemia. This is a malignant and lethal "pernicious" form of anemia (Addison-Birmer disease), which was considered incurable.

The main biochemical functions of cobalamin are the isomerization of L-glutamic acid into β-threo-3-methylaspartic acid, methylmalonyl enzyme A into succinyl coenzyme A, conversion of glycerol into β-oxypropionic aldehyde, lysine into butyric and acetic acids, ribosides into deoxyribosides; it participates in many important reactions catalyzed by it in combination with folic acid, for example, in the synthesis of nucleic bases. Dietary sources of vitamin B12 are animal tissues and legumes.

With vitamin B12 deficiency, megaloblastic (macrocytic) anemia develops. This disease is characterized by an increase in the size of erythrocytes, a decrease in the concentration of hemoglobin in the blood. The same symptoms are observed in malignant (pernicious) anemia. The reason in both cases is a violation of DNA synthesis (primarily DNA) in rapidly dividing blood cells. Megaloblastic anemia is almost always the result of a deficiency of folic acid or vitamin B12, or both.

Vitamin C, also known as ascorbic acid, antiscurvy, antiscurvy vitamin. The chemical structure of vitamin C is γ-lactone of 2,3-dehydro-L-gulonic acid. It contains a "reducton" grouping [—C(OH) = C (OH)—CO], which can be easily oxidized with the formation of dehydro-L-ascorbic acid. It is interesting that D-ascorbic acid not only does not have vitamin properties, but is also an anti-vitamin C.

The main natural sources of vitamin C are fresh vegetables and fruits, but it is also abundant in animal tissues, since most animals can synthesize this vitamin. Exceptions are only some birds, guinea pigs, monkeys and humans, who need 75-100 mg of ascorbic acid every day. In industry, L-ascorbic acid is obtained by

chemical synthesis. L-ascorbic acid, being the strongest reductant of a living organism, takes part in many biochemical processes of electron transport, and the dehydroascorbic acid formed in the process is easily restored to its original state with the help of a special reductase. Important functions of ascorbic acid are the metabolic splitting of tyrosine and lysine, hydroxylation of proline and lysine residues in the protocol agent to hydroxyproline and hydroxylysine residues, which is necessary for the construction of fibrillar collagen. It also ensures hydroxylation of dopamine to the important hormone and neurotransmitter norepinephrine, participates in lipid metabolism and many other reactions.

In medicine, ascorbic acid is widely used not only for the treatment of scurvy, but also for hemorrhagic diatheses, bleeding, including those caused by radiation sickness, a number of infectious and immune diseases, for the normalization of lipid metabolism in atherosclerosis, increased physical and mental stress, colds, as well as in chemotherapy cancer

In scurvy, collagen synthesis is disrupted at the stage of hydroxylation of proline and lysine residues. As a result, less stable and strong collagen fibers are formed. This is related to the fragility of blood vessels in scurvy and the occurrence of numerous spot hemorrhages.

Vitamin P. Under this name, a complex of flavonoid compounds is known, capable of partially relieving the severity of vitamin C deficiency, reducing the permeability and fragility of blood vessels (P — from the English permeability — permeability). Typical representatives of substances with this activity are **hesperidin,** which is found in large quantities in citrus fruits (for example, up to 8% of it is found in dried orange peel), **eriodictin, catechin, quercetin** (flavone of yellow flowers) and its glycoside **routine**. They are widely used in hypo- and avitaminosis P and in the treatment of many diseases of blood vessels (for example, "purpura disease" - thrombopenic purpura, hemorrhagic diatheses, hemorrhages in the retina of the eye, radiation sickness), as well as hypertension, measles, scarlet fever, typhus, etc.

Vitamin U. Vitamin U (S-methylmethionine, anti-ulcer factor, from Latin ulcus – ulcer). Participates in the synthesis of methionine, choline and creatine as a donor of methyl groups. Prevents or delays the development of stomach ulcers. It is contained in the juice of raw vegetables (for example, cabbage, potatoes), steamed milk, liver, carrots, onions.

Vitamin A (retinol)	It is absorbed mainly in the proximal part of the small intestine. The absorption of beta-carotene (provitamin A) is facilitated by a small amount of vitamin E, while in large concentrations it blocks the absorption of both vitamin A and its precursor.
Vitamin D (cholecalciferol)	It is absorbed in the proximal part of the small intestine. In the future, the formation of the active form of the vitamin - calcitriol occurs in two stages: in the liver and kidneys.
Vitamin E (tocopherol)	It is transported in the small intestine with the help of micelles, undergoes the stage of emulsification with bile. Adsorbed in the proximal part of the small intestine with the help of passive diffusion and possibly a specific transporter. At a high concentration of the vitamin, about 80% is absorbed, at a low concentration - 20% of the total amount of vitamin that entered the intestines. The absorption of vitamin E increases with a decrease in the consumption of vitamin D, zinc ions, magnesium, copper and selenium. High concentrations of vitamin E block the uptake of vitamin D. This may be due to the use of the same sites for diffusion across the enterocyte membrane or transporters.
Vitamin K	It is absorbed in the small intestine by passive and active diffusion. Excess vitamins A and E block absorption of vitamin K, possibly as a result of competition for the same diffusion site in the proximal small intestine. In this regard,

	the combination of vitamin K with vitamins A and E in one multivitamin pill is not advisable.

Fat-soluble vitamins

Hypervitaminosis of fat-soluble vitamins is due to the fact that, unlike water-soluble vitamins, they are able to accumulate in the body due to their lipophilic properties. Most often, the cause of hypervitaminosis is the excessive consumption of food rich in fat-soluble vitamins, or the introduction of an excessive amount of vitamin-containing preparations. Example, **hypervitaminosis A** leads to severe poisoning, manifested by nausea, vomiting, loss of consciousness and "burning" of the upper layer of the skin, inflammation of the eyes, hyperkeratosis, hair loss, dyspeptic phenomena. Thus, the inclusion in the diet of foods containing a lot of vitamin A (liver and fish oil) should be strictly controlled. An excessive amount of vitamin D3 in the body can cause **hypervitaminosis D**. This condition is characterized by excessive deposition of calcium salts in the tissues of the lungs, kidneys, heart, vessel walls, as well as osteoporosis with frequent bone fractures.

Vitamin A, which is also called vitamin A1, retinol and axerophthol (fig. 8.1).

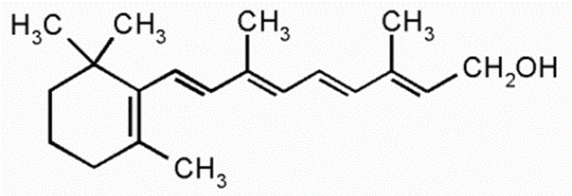


Fig. 8.1. Chemical structure of vitamin A

Retinol (in the form of complex fats, usually β-glucuronate) is found mainly in animal products, especially in the liver of marine animals and fish. A person can also satisfy his need for vitamin A through plant foods, because provitamin A - carotenes (from the Latin Daucus carota - carrot), contained in fresh vegetables and fruits, can undergo oxidative breakdown in the liver and intestinal mucosa to retinol; at the same time, symmetrically constructed β-carotene gives two retinol molecules, and α- and γ-carotene - only one each.

Vitamin A is involved in many biochemical processes, especially related to the functioning of cell membranes. The growth factor is probably not retinol, but the product of its oxidation in the liver - retinoic acid, which is also the main product of the metabolic deactivation of retinol.

The main role in visual processes is played by the products of enzymatic isomerization and oxidation of retinol - 11-cis- and all-trans-retinal. The first of them binds to the protein opsin and forms visual purple - rhodopsin, which is part of light-sensitive cells - cones and rods. During the complex process of perceiving a quantum of light and transforming it into a nerve impulse, 11-cis-retinal is isomerized as part of rhodopsin to all-trans-retinal, which after dissociation of the protein complex is restored to retinol. The inevitable losses of the latter in this cycle are replenished from the liver.

Carotene is the precursor of vitamin A1. Cleavage of carotene yields two molecules of vitamin A1 (fig. 8.2, retinol, structure b). Oxidation at C-15 converts retinol to the aldehyde, retinal (fig. 8.2, retinol, structure, c), and further oxidation produces retinoic acid (fig. 8.2, retinol, structure d), a hormone that regulates gene expression. Retinal combines with the protein opsin to form rhodopsin, a visual pigment wide spread in nature. In the dark, retinal of rhodopsin is in the 11-cis form (fig. 8.2, retinol, structure c). When a rhodopsin molecule is excited by visible light, the 11-cis-retinal undergoes a series of photochemical reactions that convert it to alltrans-retinal (fig. 8.2, retinol, structure e), forcing a change in the shape of the entire rhodopsin molecule. This transformation in the rod cell of the vertebrate retina sends an electrical signal to the brain that is the basis of visual transduction.

Vitamin A also maintains healthy skin, mucous membranes of the stomach, intestines, and bronchi. It is stored in the liver. Signs of hypovitaminosis: hemeralopia (chicken blindness) - impaired twilight vision due to a lack of visual pigment rhodopsin; pathological keratinization of the skin and mucous membranes; xerophthalmia - dryness of the cornea of the eye in connection with the blockage of the lacrimal canal as a result of keratinization of the epithelium. The daily rate of vitamin A is 1-2.5 mg, carotene is twice as much.

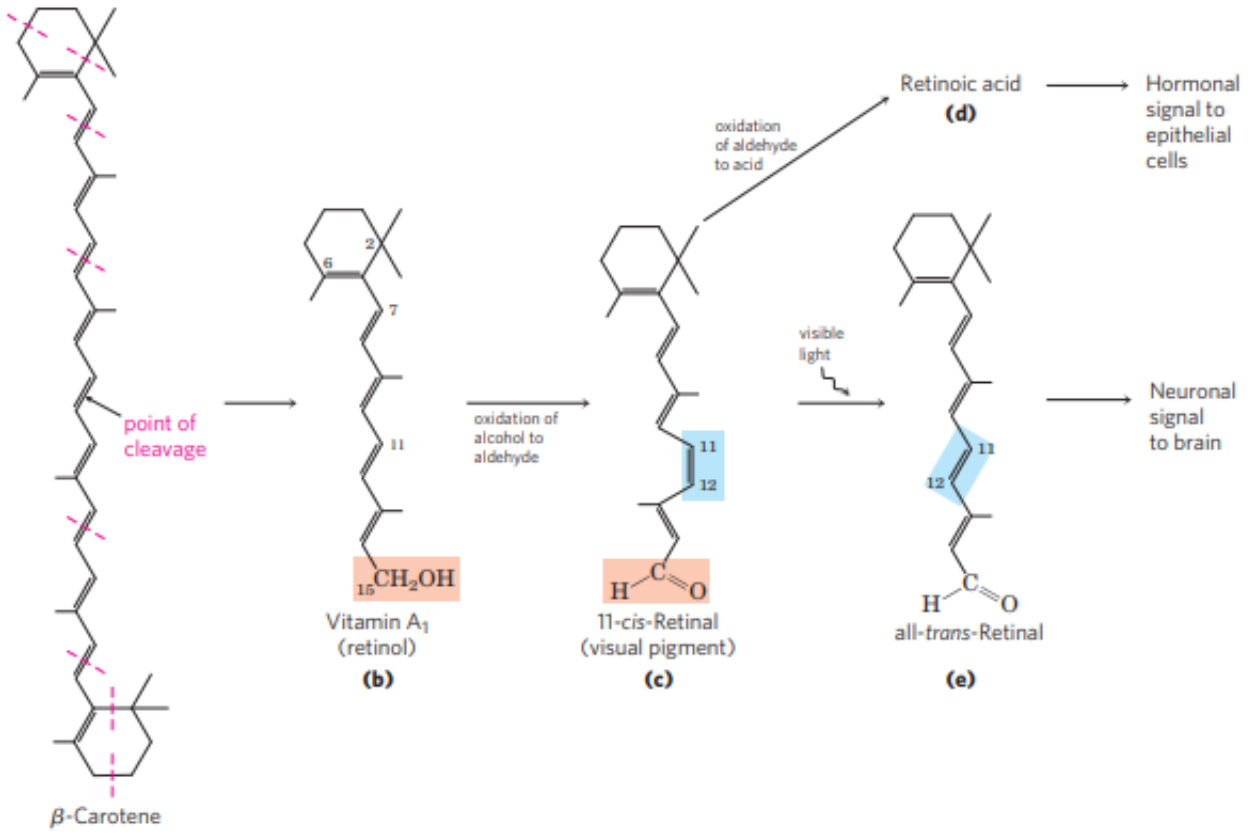


Fig. 8.2. Vitamin A1 and its precursor and derivatives

Vitamin D (cholecalciferol, antirickets) plays an important role in the process of calcium and phosphorus exchange. Vitamin D itself does not have vitamin activity, but serves as a precursor to 1,25-dihydroxycholecalciferol (1,25-dihydroxyvitamin D_3 or calcitriol, fig. 8.3). In turn, calcitriol induces the synthesis of Ca-binding proteins of enterocytes and, thus, regulates the absorption of Ca^{2+} ions in the intestines. Food sources - fish, fish oil, liver, butter, egg yolk. It can be synthesized in the human body from its precursor - 7-dehydrocholesterol under the action of ultraviolet rays (fig. 8.3).

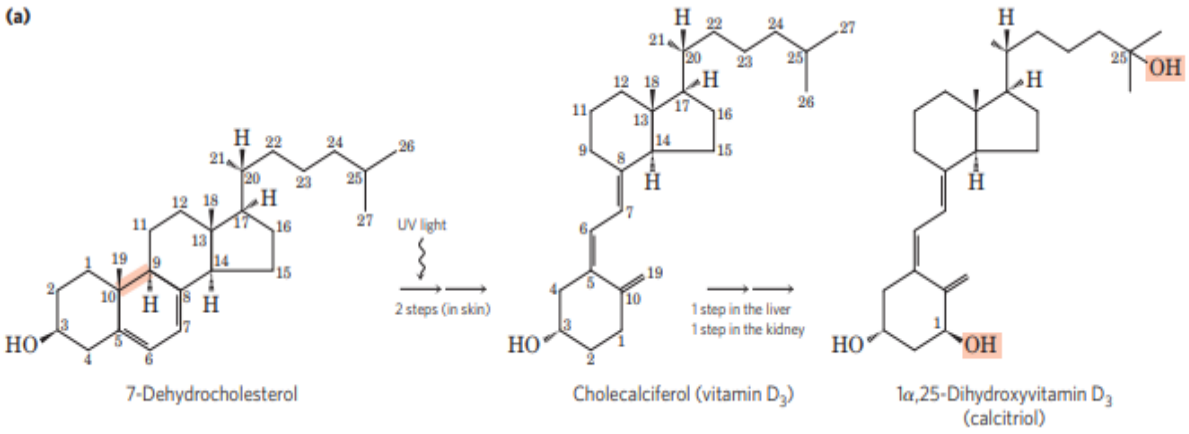


Fig. 8.3. General scheme of synthesis of vitamin D_3

With hypovitaminosis, there are disturbances in phosphorus-calcium metabolism and ossification processes. Children develop rickets ("softening" of the bones), delayed closure of the parietal bones, deformation of the chest, spine, limbs, decreased muscle tone, irritability, increased sweating, and hair loss. In adults, osteoporosis occurs - thinning of bone tissue as a result of leaching of calcium salts. With hypervitaminosis, there is intoxication, deposition of hydroxyapatite in some internal organs (calcification of kidneys, blood vessels). The daily dose of vitamin D_3 is 10-20 mg.

Vitamin E, or α-tocopherol (from Greek Τοχοζ - childbirth and Latin Phero - to carry), was discovered as an antisterile factor (fig. 8.4). The lack of vitamin disrupts the normal development of the fetus (females) and spermatogenesis (males) in rats.

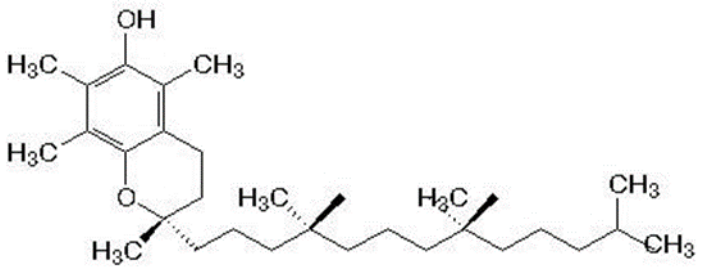


Fig. 8.4. Structure of vitamin E (α-tocopherol)

Tocopherols are synthesized only in plants. They are found mainly in seeds (wheat and rice grains) and oils (sunflower, corn, cotton, soybean, rice, hemp, palm,

etc.), as well as in green parts of plants (lettuce, spinach). In animals, the lack of tocopherol leads not only to infertility, but also to damage to the myocardium and other muscle tissues, vascular and nervous systems. The mechanism of its action is related both to the antioxidant effect, aimed at preventing the oxidation of unsaturated fatty acid residues in membrane lipids, and to the effect on the biosynthesis of enzymes, especially those involved in the construction of heme.

Hypovitaminosis of vitamin E rarely occurs in humans. The daily requirement (about 5 mg for children and 10-25 mg for adults, especially for pregnant women) is easily met with a normal diet.

Vitamin F. A group of unsaturated fatty acids - linoleic, linolenic and arachidonic - is conventionally united under this name. The need for animals (rats) in these acids is huge, because they are necessary for the construction of cell membranes. However, it should be noted that arachidonic acid (fig. 8.5) is 10 times more active than other acids of the group. It is necessary mainly for the biosynthesis of prostaglandins, prostacyclin, thromboxanes, and leukotrienes.

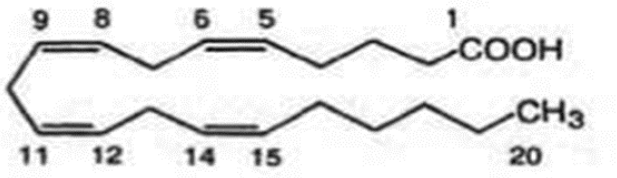


Fig. 8.5. Structure of arachidonic acid

Vitamins K - this is a large group of coagulation vitamins or antihemorrhagic vitamins (phylloquinone and menaquinones). This group of vitamins was first discovered as an antihemorrhagic factor in chickens in 1929.

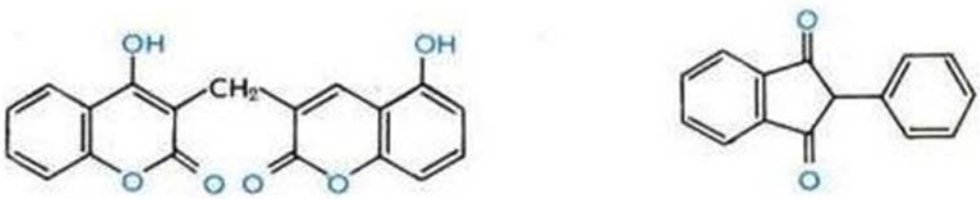
Hemorrhage is a disease that is associated with a violation of the integrity of the walls of blood vessels, with subcutaneous and intramuscular bleeding caused by a low blood clotting rate.

Vitamins K1 and K2 are necessary for a person first of all to normalize or accelerate the process of blood coagulation. They are not involved in the act of

coagulation and thrombus formation itself, but in the construction of factors II (prothrombin), VII (proconvertin), IX (antihemophilic globulin B, Christmas factor) and X (Stewart-Prover factor) of this complex system, more precisely, in γ-carboxylation of glutamic acid residues with the formation of γ-carboxylates necessary for binding calcium ions. In addition, menaquinones are mediators of some biochemical redox transformations, in particular during photosynthesis, oxidative phosphorylation and oxidation of dihydroorotic acid to orotic acid.

The green parts of plants are especially rich in vitamin K, in addition, they are produced in sufficient quantities by the intestinal microbiota. Therefore, the lack of vitamin K occurs only in newborns, in adults it can be caused by either suppression of the intestinal microbiota by sulfonamides or antibiotics, or poor absorption due to a lack of synthesis of its emulsifier - bile. Vikasol is a synthetic water-soluble analogue of vitamin K.

With some diseases (myocardial infarction, thrombophlebitis, etc.), associated with increased blood coagulation and the formation of blood clots in blood vessels, there is a need to use **antivitamins K** (anticoagulants). The most famous of them are dicoumarol, its analogues and derivatives, as well as phenylin (fig. 8.6).



Dicoumarol Phenylin

Fig. 8.5. Structure of dicoumarol and phenylin

Antivitamins

At present, it is customary to divide antivitamins into two groups:

1) antivitamins that have a structure similar to the structure of the native vitamin and that have an effect based on a competitive relationship with it;

2) antivitamins that cause modification of the chemical structure of vitamins or complicate their absorption, transport accompanied by a decrease or loss of the biological effect of vitamins.

Thus, the term "antivitamins" refers to any substances that cause, regardless of the mechanism of their action, a decrease or complete loss of the biological activity of vitamins.

Structurally similar antivitamins are antimetabolites, which upon interaction with apoenzyme form an inactive enzyme complex and turn off the enzymatic reaction with all subsequent consequences.

In addition to structural analogues of vitamins, the introduction of which causes the development of true vitamin deficiency, there are antivitamins of biological origin, including enzymes and proteins that cause splitting or binding of vitamin molecules, depriving them of their physiological effect. These include, for example, thiaminases I and II, which cause the breakdown of the vitamin B1 molecule; ascorbate oxidase, which catalyzes the destruction of vitamin C; avidin protein, which binds biotin into a biologically inactive complex. Most of these antivitamins are used as drugs with a clearly directed effect on some biochemical and physiological processes. In particular, dicoumarol, warfarin and tromexan (antagonists of vitamin K) are used as anticoagulant drugs from the antivitamins of fat-soluble vitamins. Well-studied thiamine antivitamins are oxythiamine, pyri- and neopyrithiamine; riboflavin - aterbin, acrichin, galactoflavin, isoriboflavin (all of them compete with vitamin B2 in the biosynthesis of FAD and FMN coenzymes); pyridoxine (vitamin B6) - deoxypyridoxine, cycloserine, isonicotinoyl hydrazide (isoniazid), which has an antibacterial effect on the tubercle bacillus (forms a false coenzyme NAD+). Antivitamins of folic acid are amino- and amethopterins; vitamin B12 - 2-aminomethylpropanol-B12 derivatives; nicotinic acid - isoniazid and 3-acetylpyridine; para-aminobenzoic acid - sulfonamide preparations; all of them are widely used as antitumor or antibacterial agents that inhibit the synthesis of protein and nucleic acids in cells.

2. TASKS FOR INDEPENDENT WORK.

In the table with test tasks, underline the key words, choose the correct answer and justify it:

1.	The patient was diagnosed with: pain along the course of large nerve trunks and an increased content of pyruvate in the blood. The lack of which vitamin can cause such changes? A. B1 B. PP C. Pantothenic acid D. B2 E. Biotin	
2.	Most of the participants of Magellan's expedition to America died from vitamin deficiency, which was manifested by general weakness, subcutaneous hemorrhages, tooth loss, and bleeding gums. Enter the name of this vitamin deficiency: A. Scurvy (scurvy) B. Birmer's anemia C. Polyneuritis (beri-beri) D. Pellagra E. Rickets	
3.	Hypovitaminosis B1 is often observed in patients with	

	alcoholism, which is a consequence of nutritional disorders. Symptoms of hypovitaminosis B1 are disorders of the nervous system, psychosis, memory loss. Why are nervous tissue cells particularly sensitive to vitamin B1 deficiency? A. The oxidation of fatty acids is disturbed B. Lipolysis of adipose tissue increases C. The intensity of glycolysis increases D. The intensity of glycolysis decreases E. Aerobic decomposition of glucose is disturbed	
4.	Sulfanilamide drugs are structurally similar to para-aminobenzoic acid. What is the molecular basis of their pharmacological effect? A. Violation of vitamin synthesis B. In the destruction of the cell membrane C. In the activation of lipolysis D. In the inhibition of glycolysis E. In binding to DNA	

5.	The patient was diagnosed with megaloblastic anemia. An insufficient amount of which substance can lead to the development of this disease? A. Cholecalciferol B. Magnesium C. Cyanocobalamin D. Midi E. Glycine	
6.	A 10-year-old girl often suffers from acute respiratory infections, after which multiple point hemorrhages are observed in places where clothes rub. Hypovitaminosis of which vitamin takes place? A. B2 B. S C. A D. B1 E. B6	
7.	During the visit, the doctor found symmetrical roughness of the cheeks, diarrhea, and nervous disorders in the child. The lack of which nutritional factors is the cause of this condition? A. Lysine, ascorbic acid	

	B. Methionine, lipoic acid C. Threonine, pantothenic acid D. Phenylalanine, pangamic acid E. Nicotinic acid, tryptophan	
8.	The patient has frequent bleeding from internal organs and mucous membranes. The analysis revealed a deficiency of hydroxyproline and hydroxylysine in the composition of collagen fibers. Due to the lack of which vitamin in the patient's body, the processes of hydroxylation of the named amino acids are disturbed? A. Vitamin A B. Vitamin H C. Vitamin C D. Vitamin K E. Vitamin PP	
9.	Polyneuritis (beri-beri disease) was detected in a woman who has been on a diet using refined rice for a long time. The lack of which vitamin in the diet leads to the development of this disease? A. Tiamine B. Pyridoxal	

	C. Ascorbic acid D. Riboflavin E. Folic acid	
10.	A patient with symmetrical dermatitis of open areas of the skin came to see a doctor. During the conversation with the patient, it was established that he eats mainly cereals and eats little meat, milk and eggs. Deficiency of which of the listed vitamins dominates in this patient? A. Calciferol B. Nicotinamide C. Folic acid D. Tocopherol E. Biotin	
11.	Acrychin is prescribed for enterobiosis - a structural analog of vitamin B2. Violation of the synthesis of which enzymes in microorganisms does this drug cause? A. Cytochrome oxidases B. Aminotransferases S. Peptidases D. FAD-dependent dehydrogenases	

	E. NAD-dependent dehydrogenases	
12.	Taking into account the clinical picture, the patient was prescribed pyridoxal phosphate. What processes is this drug recommended for correction? A. Deamination of purine nucleotides B. Transamination and decarboxylation of amino acids C. Synthesis of purine and pyrimidine bases D. Oxidative decarboxylation of keto acids E. Protein synthesis	
13.	After the surgical removal of a part of the stomach, the patient's absorption of vitamin B12 was impaired, it is excreted in feces, and anemia developed. What factor is necessary for the absorption of this vitamin? A. Hydrochloric acid B. Gastrin C. Pepsin D. Gastromucoprotein E. Folic acid	
14.		

	As a result of vitamin B1 deficiency, the oxidative decarboxylation of α-ketoglutaric acid is disturbed. The synthesis of which of the following coenzymes is disrupted in this case? A. Flavinadenine dinucleotide B. Coenzyme A C. Thiamine pyrophosphate D. Lipoic acid E. Nicotinamide adenine dinucleotide	
15.	A 9-month-old child is on artificial feeding. Mixtures are used for feeding, which are not balanced in terms of vitamin B6 content. The child has pellagra-like dermatitis, convulsions, and anemia. The development of seizures may be associated with a violation of the formation of: A. Serotonin B. Histamine C. GABA D. Dopamine E. DOFA	
16.	The patient has an increased concentration of pyruvate in the	

	blood. A significant amount of it is excreted in the urine. What vitamin deficiency is observed in the patient? A. B3 B. B2 C. B1 D. B6 E. E	
17.	After a course of therapy, the doctor suggests a man with duodenal ulcer to consume cabbage and potato juices. The content of which substances in these vegetables contributes to the prevention and healing of ulcers: A. Vitamin B1 B. Vitamin C C. Vitamin U D. Pantothenic acid E. Vitamin K	
18.	After removing 2/3 of the patient's stomach, the hemoglobin content in the blood decreased, the number of erythrocytes, and the size of these blood cells increased. Deficiency of which vitamin leads to such changes in the blood? A. P	

	B.C C. B12 D. PP E. B6	
19.	For the treatment of some infectious diseases caused by bacteria, sulfonamide drugs that block the synthesis of the bacterial growth factor are used. Name the mechanism of their action: A. Take part in redox processes B. Are allosteric enzymes C. Inhibit the absorption of folic acid D. They are allosteric enzyme inhibitors E. They are para-aminobenzoic acid antivitamins	
20.	A 36-year-old woman developed hypovitaminosis B2. The reason for the appearance of specific symptoms (damages to the epithelium, mucous membranes, skin, cornea of the eye) is probably a deficiency: A. Cytochrome Z B. Cytochrome A1 C. Cytochrome B	

	D. Flavin coenzymes E. Cytochrome oxidases	
21.	A 37-year-old patient, against the background of long-term use of antibiotics, has increased bleeding with minor injuries. In the blood - a decrease in the activity of II, VII, X blood coagulation factors; increase in the duration of blood coagulation. These changes are associated with an insufficient amount of which vitamin? A. Vitamin E B. Vitamin C C. Vitamin A D. Vitamin D E. Vitamin K	
22.	A pregnant woman with a history of several miscarriages was prescribed therapy containing vitamin preparations. Name the vitamin that contributes to bearing a child: A. α-tocopherol V. Rutin C. Folic acid D. Pyridoxal phosphate E. Cyanocobalamin	

23.	In a child in the first year of life, during a preventive examination, a violation of bone mineralization was detected. Lack of which vitamin can cause this? A. Folic acid B. Tocopherol C. Calciferol D. Cobalamin E. Riboflavin	
24.	A 6-month-old child has frequent and intense subcutaneous hemorrhages. The appointment of a synthetic analogue of vitamin K (Vikasol) gives a positive effect. In the γ-carboxylation of glutamic acid, which protein of the blood coagulation system is this vitamin involved in? A. Rosenthal factor B. Antihemophilic globulin A C. Fibrinogen D. Prothrombin E. of the Hageman factor	
25.	The patient has hemeralopia (chicken blindness). Which of the listed substances will have a	

	therapeutic effect? A. Carnitine B. Keratin C. Creatine D. Carotene E. Carnosine	
26.	After removal of the gallbladder, the patient has complicated absorption of Ca^{2+} ions through the intestinal wall. The appointment of which vitamin will stimulate this process? A. S B. PP C. K D. B12 E. D3	
27.	Treatment of a child suffering from rickets with the help of vitamin D3 does not give positive results. What is the most likely cause of treatment failure? A. Lack of lipids in food B. Violation of transport of vitamin D3 by blood proteins C. Violation of hydroxylation of vitamin D3 D. Violation of the inclusion of	

	vitamin D3 in the enzyme E. Increased utilization of vitamin D3 by intestinal microbiota	
28.	A 39-year-old man has an increased risk of developing infectious processes, hyperkeratosis, and impaired twilight vision. What vitamin preparation should be prescribed? A. Retinol acetate B. Pyridoxine hydrochloride C. Tocopherol acetate D. Riboflavin E. Ergocalciferol	
29.	A patient who underwent a mastectomy due to breast cancer was prescribed a course of radiation therapy. Which of the listed vitamin preparations has a pronounced radioprotective effect due to antioxidant activity? A. Ergocalciferol B. Riboflavin C. Folic acid D. Tocopherol acetate E. Thiamine chloride	
30.	To prevent postoperative bleeding, a 6-year-old child is recommended	

	to take Vikasol, which is a synthetic analogue of vitamin K. What post-translational changes in blood coagulation factors are stimulated by Vikasol? A. Carboxylation of glutamic acid B. Polymerization C. Partial proteolysis D. Glycosylation E. Phosphorylation of serine radicals	
31.	A man who did not consume fats with food for a long time, but received a sufficient amount of carbohydrates and proteins, developed dermatitis, poor wound healing, and impaired vision. Deficiency of which components is the cause of metabolic disorders? A. Palmitic acid B. Vitaminiv PP, N C. Vitamins A, D, E, K D. Mineral salts E. Oleic acid	
32.	In patients with obstruction of the biliary tract, blood coagulation is inhibited, bleeding occurs, which is a consequence of insufficient	

	absorption of the vitamin: A. D B. A C. Carotene D. K E. E	
33.	Plasma blood coagulation factors undergo post-translational modification with the participation of vitamin K. As a cofactor, it is required in the enzyme system of γ-carboxylation of protein blood coagulation factors, due to the increased affinity of their molecules with calcium ions. Which amino acid is carboxylated in these proteins? A. Serin B. Valin C. Arginine D. Glutamic acid E. Phenylalanine	
34.	During the examination of the child, the doctor found signs of rickets. The lack of which compound in the child's body contributes to the development of this disease?	

	A. Biotin B. Retinol C. 1,25-[OH]-dihydroxy-cholecalciferol D. Naphthoquinone E. Tocopherol	
35.	As a result of post-translational changes of some proteins involved in blood coagulation, in particular prothrombin, they acquire the ability to bind calcium. Vitamin participates in these changes: A. Vitamin B1 B. Vitamin A C. Vitamin B2 D. Vitamin C E. Vitamin K	
36.	In clinical practice, the drug isoniazid is used for the treatment of tuberculosis - an anti-vitamin that is able to penetrate the tubercle bacillus. The tuberculostatic effect is due to the violation of replication processes, redox reactions due to the formation of a false coenzyme: A. FAD B. FMN C. OVER+	

	D. TDF E. KoQ	
37.	Hemorrhages are observed in the patient, the concentration of prothrombin in the blood is reduced. The lack of which vitamin led to a violation of the synthesis of this blood coagulation factor? A. D B.C C. K D. E E. A	
38.	A 47-year-old patient with a diagnosis of "focal tuberculosis of the upper lobe of the right lung" receives isoniazid as part of combined therapy. After some time, the patient began to complain of muscle weakness, impaired vision, and coordination of movements. What vitamin preparation should be used to eliminate these phenomena? A. Vitamin A B. Vitamin B12 C. Vitamin C D. Vitamin B6	

	E. Vitamin D	
39.	It is known that the introduction of the drug dicoumarol into the human body causes a sharp decrease in the content of prothrombin and a number of other protein factors of blood coagulation in the blood. Dicoumarol is an antivitamin of which vitamin? A. Vitamin K B. Vitamin C C. Vitamin E D. Vitamin R E. Vitamin H	

3. <u>LITERATURE. Look page 320.</u>

LESSON №9

9. TOPIC: BIOCHEMISTRY OF BONE TISSUE AND TOOTH TISSUES. MINERAL AND ORGANIC COMPONENTS OF TOOTH TISSUES. MINERALIZATION, DEMINERALIZATION AND REMINERALIZATION

1. INFORMATION MATERIAL.

To perform its biological function, some types of connective tissue must have high mechanical strength. This quality is achieved due to the high content of mineral substances in them. There are 4 types of mineralized (hard) tissues in the human body: bone, cementum, dentine and enamel. The first three tissues are of mesenchymal origin, and enamel is of ectodermal origin.

Bone tissue consists of three main components: cells, organic matrix and mineral substances. The basis of the bone consists of collagen fibers, which are impregnated with mineral salts and are assembled into plates consisting of layers of longitudinal and transverse fibers; elastic fibers (Sharpé fibers) are also found in the bone substance.

Calcium, phosphates and carbonates are the main ones **inorganic components of bone tissue.** Of the 2.2 kg of calcium available in the body, 99% is concentrated in the bones, and 87% of phosphorus is also there.

With increased resorption processes, these elements are easily mobilized and enter the blood, where their concentration is strictly regulated and amounts to 2.1-2.6 mmol/l for common Ca^{2+} and 1-1.5 mmol/l for phosphorus. In addition, magnesium, sodium and potassium make up a significant part. 50% Mg^{2+} and 46% Na^{+} are concentrated in bone tissue. Many other ions are present in very small amounts (tab. 9.1).

It is important to note that the inorganic substances of the bone have the correct position in the form of apatite crystals with a width of 20-50A and a length of up to 500A. The result of such a structure is the formation of a large surface of

bone tissue (200 m/g), which in turn ensures the constancy of the composition and metabolic processes of bone tissue.

Table 9.1

Qualitative and quantitative composition of macroelements of mineralized tissues

Elements	g/per 100 g of fabric (gram percentage)			
	Enamel	Dentine	Cement	Bone (compact layer of tubular bone)
Ca^{2+}	32-39	26-28	21-24	24
PO_4^{3-}	16-18	12-13	10-12	11
CO_3^{2-}	1,9-3,6	3,0-3,5	2,0-4,3	3,9
Na^+	0,25-0,9	0,6-0,8	-	0,8
Mg^{2+}	0,25-0,56	0,8-1,0	0,4-0,7	0,3
Cl^-	0,19-0,3	0,3-0,5	-	0,01
K^+	0,05-0,3	0,02-0,04	-	0,2
fluorides	0,5	0,1	-	0,5
Ca/P	1,5-1,68	1,6-1,7	1,6-1,7	1,6-1,7

Organic substances of bone tissue

The organic substance of bones consists of approximately 90-95% of various types of collagen (tab. 9.2), from 3% to 8% of the mass is accounted for by non-collagenous bone proteins (tab. 9.3) and phospholipids, 1% consists of acidic and neutral glycosaminoglycans, which as a connecting substance are located between hydroxyapatite (HAP). Sometimes Ca^{2+} ions in HAP can be changed to Ba, Sr. Rarely on Na, K, Zn. Such isomorphic substitutions lead to a decrease in caries resistance. Chondroitin sulfate plays a major role in bone metabolism. It forms the

main substance of bones with proteins and is of great importance in the exchange of calcium. Bone tissue also reveals a large amount of citrate .

Table 9.2

Types of collagen in different fabrics

Fabrics	**Types of collagen**
Enamel	I, III
Dentine	I, III, IV, V, VI
Cement	I, II, III, V, IX, XII, XIV
Pulp	I, III, V, VI
Cartilage	II, VI, IX, XII, XIV
Bone	I, III, IV, V, VI

Table 9.2

The most important non-collagenous proteins (NCB) of the bone matrix and their functions.

Proteins	Functions
Glycoproteins	
Osteonectin	Glycosylated, phosphorylated protein; multiple low affinity to Ca^{2+}
Alkaline phosphatase	Ca^{2+} binding
BAG-75	Contains 60% carbohydrates (7% - sialic acid), 8% phosphates
Proteins that have in the composition RGD (RGD – the amino acid sequence arginine-glycine-aspartate, with which proteins attach to cell receptors)	
Thrombospondin	Binding of Ca^{2+} and hydroxyapatite, binding sites are the same as fibronectin; binds to osteonectin; cell adhesion

Fibronectin	Binding sites with cell surface, fibrin, heparin, bacteria, gelatin, collagen, DNA; initial attachment of cells
Vitronectin	It binds to many matrix and serum proteins responsible for cell attachment
Osteopontin	The product of the secretion of developing osteoblasts is able to bind strongly to hydroxyapatite; enhances the proliferation of neighboring osteoblasts.
Bone sialoprotein	Contains 50% carbohydrates (12% - sialic acid); in some species, tyrosine sulfation occurs; participates in cell attachment
Proteins containing γ-carboxyglutamic acid	
Gla-protein matrix (Gla - glycosaminoglycans)	One S-S intramolecular bond, 5 gla residues
Osteocalcin	The main calcium-binding protein of the intercellular matrix of bone, which does not belong to collagens. It is secreted by osteoblasts at the stage of mineralization, the process of rebuilding bone tissue. When its function is disturbed, destruction of enamel develops.

Nucleic acids

Both types of nucleic acids are present in bone tissue, but the amount of RNA exceeds the amount of DNA by 1.5-2.0 times. The intensity of formation of the organic matrix of bone tissue correlates with the concentration of RNA in osteoblasts, since the amount of RNA in cells reflects the activity of their biosynthetic processes.

Lipids

Among the lipids of bone tissue, glycerophospholipids (GPL) are the most important. A significant amount of GPL is contained in osteoblasts, which actively synthesize and excrete them into the extracellular space. The rest of phosphoric acid or -COO-group, located in the GFL molecule, are negatively charged and capable of attaching Ca^{2+}. Some studies highlight that it is GFLs that play a leading role in the initial stages of mineralization, binding Ca^{2+}; in the implementation of continuous growth of HAP crystals, as well as in the implementation of the function of mediators for the complexation of HAP from the protein matrix.

Carbohydrates

Carbohydrates in bone tissue are localized intracellularly. Intracellular carbohydrates are represented by glycogen, and extracellular glycosaminoglycans.

Glycogen and glucose usually perform an energy function. Adenosine triphosphate formed from the breakdown of glucose is used for mineralization.

Citrate

It is present in bone tissue in a relatively large amount - up to 1% of the total mass, which is 20 times more than in the liver, and the activity of the enzyme citrate synthase, which catalyzes the formation of citrate from acetyl-CoA and oxaloacetate, in bone tissue is much higher than the activity of other enzymes Citrate is involved in metabolic processes in bone tissue, mainly in the exchange of Ca^{2+}.

The structure and functions of bone tissue cells

Osteoblasts are formed from undifferentiated mesenchymal stem cells in the developing bone tissue; capable of proliferation. Osteoblasts synthesize and release proteins into the intercellular space (primarily ***collagen***, and ***osteocalcin and osteopontin) and glycosaminoglycans***, forming ***organic matrix*** bone tissue. Then, with the help of the secretion of alkaline phosphatase and the release of calcium salts, they provide ***mineralization of the intercellular substance***. Gradually,

releasing the intercellular substance, they become bricked up and turn into ***osteocytes***. At the same time, intracellular organelles are significantly reduced, synthetic and secretory activity decreases, and the functional activity characteristic of osteocytes is preserved.

Osteocytes – the main cells of the formed bone tissue, formed from osteoblasts. They are their definitive forms and are not divisible. The activity of osteocytes is insignificant and consists in ***metabolism support*** between cells and intercellular substance.

Osteoclasts – bone-destroying cells, which are not their own bone cells, but are of monocytic origin (formed from the hematopoietic tissue of the bone marrow) and belong to the macrophage system.

There are no osteoclasts in the formed mature bone, but since local bone tissue remodeling processes are continuously carried out during ontogenesis, they are found in places of bone destruction and regeneration, as well as in the periosteum.

Mechanism of bone tissue and teeth mineralization

In a mature organism, the processes of bone mineralization and resorption are in a state of dynamic equilibrium. Mineralization is the formation of crystal structures of mineral salts of bone tissue. Osteoblasts take an active part in this process. Mineralization requires a lot of energy (in the form of ATP). It is also important to add that the mineralization process is possible only in the presence of strictly oriented collagen fibers.

The order of bone mineralization.

Osteoblasts secrete molecules ***collagen and the main substance***.

Collagen molecules form collagen fibers, which are called ***osteoids***.

Osteoblasts secrete an enzyme – ***alkaline phosphatase***, which increases the local concentration of phosphate, activates collagen fibers, causing the deposition of calcium phosphate salts. The optimal pH level for alkaline phosphatase is 8.6-10.1.

This enzyme is activated by Mg^{2+}, Co^{2+}, Mn^{2+} ions, and inhibited by oxalates, cyanides, glutamic acid, phosphates, and cysteine.

Calcium phosphate salts precipitate on collagen fibers and finally become ***hydroxyapatite crystals***.

Two main stages of mineralization can be distinguished:

1st stage consists in the formation of initial hydroxyapatite crystals inside the matrix vesicles. This process is controlled by phosphatase (including alkaline phosphatase), as well as calcium-binding molecules (phospholipids and proteins), which are abundant in matrix vesicles. A feature of the mineralization process is the oversaturation of the medium with calcium and phosphorus ions, which ensures their precipitation. Osteoblasts begin to synthesize ***chondroitin sulfates and bone collagen***. Collagen is the matrix for the mineralization process - calcium and phosphorus are combined with it. An obligatory participant in the process is complex lipids.

2nd stage consists in the rupture of the membranes of the matrix vesicles with the release of the formed crystals into the extracellular space, where their further reproduction is controlled by the conditions of the extracellular microenvironment. They have an important role ***proteases and membrane phospholipases***, which ensure the rupture of membranes and the release of minerals.

Forms of bone tissue metabolism disorders. Ways of metabolic correction of osteoporosis.

Disruption of bone tissue metabolism is mainly associated with a violation of phosphorus-calcium metabolism. Typical disorders are: hypercalcemia, hypocalcemia, hyperphosphatemia, hypophosphatemia, fluorosis (excess intake of fluoride with food), **osteolaterism, osteoporosis**.

Osteolaterism – characterized by changes in the metabolism of connective tissue, weakening of connections between epiphyseal plates (growth zone) and bone. The development of this pathology is associated with a deficiency of hydroxylysine. In the body, hydroxylysine is formed from lysine under the influence of the enzyme lysylhydroxylase.

Osteoporosis – one of the most common metabolic diseases. There is a classification of osteoporosis according to which primary and secondary osteoporosis are distinguished.

Primary osteoporosis divided into postmenopausal (natural menopause) and senile (senile).

Secondary osteoporosis develops as a result of various diseases. The following forms are distinguished:

1. Endocrine genesis (with Itsenko-Cushing's disease, excess production of PTH, insulin deficiency);

2. It develops in various diseases of the gastrointestinal tract, liver, kidneys, and alcoholism;

3. Osteoporosis caused by dietary factors (calcium deficiency, insufficient protein intake, ascorbic acid deficiency).

Metabolic correction of osteoporosis includes pathogenetic, aimed either at slowing down increased bone resorption (calcitonin, sex hormones - estrogens, androgens, progestins), or at stimulating bone formation (parathyroid hormone, glucocorticoids, thyroid hormones); or for the normalization of both processes, as well as for the elimination of vitamin D deficiency.

Diagnostic criteria of bone tissue metabolism.

To assess the activity of the processes of bone formation and resorption, calcium-regulating hormones, markers of bone metabolism are determined, and the morphological characteristics of bone tissue are evaluated.

Markers of bone tissue formation used to assess bone metabolism, that is, the enzymatic activity of osteoclasts and osteoblasts, or the level of bone matrix components that enter the circulation system in the process of bone tissue formation or resorption.

Alteration of bone metabolism may be important in osteoporosis, Paget's disease, bone tumors, and chronic inflammatory joint diseases. Such markers include alkaline phosphatase, osteocalcin, propeptide of type 1 procollagen.

Alkaline phosphatase characterizes the activity of osteoblasts. Participates in the extracellular destruction of pyrophosphate - an inhibitor of calcium phosphate deposition.

Osteocalcin (gla protein) – non-collagenous protein of the bone matrix, which is synthesized by osteoblasts. The concentration of osteocalcin in the blood plasma is used in clinical practice as an indicator of the intensity of the metabolism of osteoblasts in the diagnosis of various diseases with disturbances in the metabolism of mineral substances.

Propeptides of type 1 procollagen – C- and N-propeptides. Since collagen is the most common organic component of the bone matrix, the level of the propeptide in the bloodstream can reflect the level of bone formation.

Markers of bone tissue resorption.

An important component of collagen is **hydroxyproline**, which is about 13% of the total amino acid composition of this protein. Because approximately half of the collagen in the human body is found in bone, urinary hydroxyproline excretion reflects bone resorption, but up to 40% of urinary hydroxyproline may be of non-bone origin. The nature of the relationship between the excretion of hydroxyproline with urine and the metabolism of bone tissue is complex. Hydroxyproline, released as a result of the destruction of collagen in the tissues, after filtration in the glomeruli of the kidneys is reabsorbed in the tubules, then undergoes oxidation in the liver to carbon dioxide and urea. Only 10% of hydroxyproline is excreted in the urine. Thus, this method is not essential for diagnosing osteoporosis and evaluating the effectiveness of its therapy and prevention.

Acid phosphatase – a lysosomal enzyme present in bone, prostate, platelets, red blood cells, and spleen. An increase in its level is noted in various metabolic bone diseases, which are accompanied by an increase in the turnover of bone tissue.

Pyridinoline and deoxypyridinoline are components of type 1 collagen. They are released in the process of degradation of the bone matrix, are not reabsorbed in the renal tubules, do not undergo further metabolism and are detected in the urine.

Pyridinoline and, especially, deoxypyridinoline are considered more sensitive and specific markers of bone resorption. Their excretion in urine increases significantly with osteoporosis.

Tooth structure

It is known that three types of dense tissues are involved in the construction of a tooth: enamel, dentin and cementum. These tissues in the tooth have different localization. In addition, there is dental pulp, which is similar to bone marrow. These components differ from each other in their chemical composition and histological structure (tab. 9.3).

Table 9.3

The percentage content of various substances in the hard tissues of the tooth and bones

	Mineral substances	Organic substances	Water
Enamel	95%	1-1,5%	4%
Dentine	70%	20%	10%
Cement	50%	27%	13%
Bone	45%	30%	25%

Tooth enamel – the hardest tissue of the human body. It is a unique avascular and acellular bioceramic material with a complex structure and exceptional mechanical properties (combination of high hardness with significant elasticity). The specified properties ensure its function - protection of dentin and pulp from external mechanical, chemical and temperature stimuli, thanks to which the teeth fulfill their purpose - bite off and grind food. These features of enamel are acquired in the process of phylogenesis.

The mineral substances of tooth enamel are mainly represented by various forms of apatites (tab. 9.4), as well as some other salts. In the composition of all

inorganic enamel compounds, there are mainly two elements: calcium, which is 37%, and phosphorus - 17%.

Table 9.4

Basic mineral combinations of enamel

Mineral combinations	%
hydroxyapatite	75,04
carboxyapatite	12,06
chlorapatite	4,39
fluorapatite	2,03
calcium carbonate	1,68
magnesium carbonate	1,33
other salts	3,47

Dentine, which constitutes the main mass of the tooth. It contains 70-72% inorganic and 28-30% organic substances and water. The basis of the inorganic substance is calcium phosphate (hydroxyapatite), calcium carbonate and, in a small amount, calcium fluoride. It also contains many macro- and microelements.

Dentin is formed by odontoblasts. This tissue is denser and harder than cement and bones, due to the higher (up to 70%) content of mineral components. Odontoblasts are not embedded in the organic matrix, unlike osteocytes and cementoblasts. They are constantly on the surface that separates dentin and pulp. New odontoblasts are formed from the parenchymal cells of the pulp throughout life. Thus, the oldest dentin will be located on the border with the enamel, and morphogenesis is actively taking place on the border with the pulp. The transformation of pulp mesenchymal cells into odontoblasts is regulated by MBK protein (bone morphogenetic protein), the concentration of which is higher in dentin than in bone tissue.

The formation, mineralization and decay of dentin takes place in the same way as in bone tissue. At the same time, dentin differs from the latter in the features of

its protein composition and the speed of some metabolic processes. Thus, matrix Gla protein is absent in dentin, but in addition to type 1 collagen and osteonectin, which are subject to mineralization, there is a specific protein phosphophorin, which is synthesized by odontoblasts.

The organic substance of dentin consists of proteins, lipids and polysaccharides. The amino acid composition of proteins is typical for collagen: a large amount of glycine, proline, oxyproline and the absence of sulfur-containing amino acids.

The main substance of dentin is penetrated by a large number of dentinal tubules, the number of which ranges from 30,000 to 75,000 per 1 mm2 of dentin. Dentinal fluid circulates in the dentinal tubules (tubules), which delivers organic and inorganic substances involved in the renewal of dentin.

Cement - the tissue layer covering the tooth root consists of 68% inorganic and 32% organic substances. Cells that form cement are called cementoblasts. Cementoblasts are surrounded by a mineralized matrix, similar to osteocytes. In a mature tooth, there are no vessels, cementoblasts are found in single specimens only in the lower part, thus, cementum is a metabolically inert tissue. The composition of the organic matrix of cement is similar to the composition of bone tissue: the amount of collagen and non-collagen proteins is slightly lower and the proportion of mineral components is higher. Mineralization processes proceed similarly.

In terms of chemical composition and structure, cement resembles coarse-grained bone. The main substance of the cement, impregnated with calcium salts, is permeated with collagen fibers, which connect with the same fibers of the bone tissue of the alveolus.

Acellular cement located on the entire surface of the root is distinguished, and cellular cement covers the top of the root, and in multi-rooted ones - the bifurcation area. Unlike bone, cement does not have blood vessels.

Mineralization, demineralization, remineralization

Dental caries is one of the most common dental diseases. Despite numerous studies, the etiology and pathogenesis of this disease are not completely clear. It is

considered common knowledge that the initial stage of the carious process is the demineralization of tooth enamel, which occurs as a result of acidic and other factors in the oral cavity. Therefore, the mineralization of the enamel determines the high resistance of the tooth enamel to acids.

Demineralization. This process occurs only in the area of the carious spot. The processes of demineralization, especially expressed in the subsurface layer of enamel, lead to changes in the organic matrix and an increase in the permeability of enamel. This is due to an increase in the microspace between hydroxyapatite crystals and greater solubility of enamel in an acidic environment. Therefore, the main role in demineralization processes is assigned to organic acids. 2 types of demineralization reactions are possible, depending on the acidity:

$$1)\ Ca_{10}(PO_4)_6(OH)_2 + 8H^+ \rightarrow 10\ Ca^{2+} + 6HPO_4^{2-} + 2H_2O$$

$$2)\ Ca_{10}(PO_4)_6(OH)_2 + 2H_3O^+ \rightarrow Ca_9(H_3O)_2(PO_4)_6(OH)_2 + Ca^{2+}.$$

In hydroxyapatites, which determine the structure of tooth enamel, the content of its main mineral components - Ca and P, is variable. The Ca/P molar ratio ranges from 1.3 to 2.0. At the same time, it is believed that the greater the Ca / P ratio, the greater the hydroxyapatite of the tooth enamel is able to resist the action of acids. It is possible to stimulate the reaction of the first type and inhibit demineralization.

Remineralization — this is a partial change or complete restoration of the mineral components of the tooth enamel due to the components of saliva or remineralizing solutions. Remineralization is based on the adsorption of mineral substances in carious areas. The criterion for the effectiveness of remineralizing solutions is the restoration of the following enamel properties: permeability, solubility, disappearance or reduction of carious spots, etc. It's saliva. In addition, remineralizing solutions are used, which contain Ca, P and all the necessary trace elements in the same proportions and quantities as in saliva.

It can be attributed to the remineralization reaction substitution reaction: HO on F- and the formation of hydroxyfluoroapatites or fluorapatites.

$$Ca_{10}(PO_4)_6(OH)_2 + 2\ F^- \rightarrow Ca_{10}(PO_4)_4\ (CO_3)_3(F^-)_2 + 2\ OH^-$$

Remineralizing solutions have a significant effect than mixed saliva. In the composition of saliva, Ca and P combine with organic complexes of saliva, and the content of these complexes in it decreases. These solutions should contain F in the required amount, because it affects the rejuvenation of Ca and P in the hard tissue of the tooth and bone. At an increased concentration, precipitation of hydroxyapatite from saliva occurs, in the absence of F, precipitation of hydroxyapatite does not occur, and calcium orthophosphate is formed instead of hydroxyapatite. With an excess of fluorine, the disease "endemic fluorosis" can occur. It is characterized by "mottling of enamel" - pigment spots or stripes. Penetration of ions from the surface into the interior of the crystal - ***(internal crystal exchange)***, occurs very slowly (days, weeks, months), and as the ions penetrate, the speed of this stage slows down even more. Only certain ions Ca^{2+}, Sr^{2+}, Pa^{2+}, F^{-} have this ability.

Hormonal regulation of the processes of mineralization and demineralization of tooth tissues (The influence of vitamins and hormones on the processes of mineralization and demineralization of tooth tissues):

1. Vitamin D (calciferol). 1,25-dioxyvitamin D_3 (active form of vit D) enhances the effect of parathyroid hormone in bone tissue and kidneys, also improves calcium absorption in the intestine.

In the case of D_3 deficiency, hypocalcemia develops with subsequent disruption of the calcification of the hard tissues of the tooth and the formation of an inferior crystal lattice of hydroxyapatite.

2. Vitamin C promotes hydroxylation of proline and lysine during collagen synthesis.

3. a) Parathyroid hormone increases the calcium content in the blood, stimulating bone resorption by osteoclasts. It also affects the maturation processes of D_3 in the kidneys.

b) Calcitonin is an antagonist of parathyroid hormone. It reduces the calcium content in the blood, stimulating excretion in the urine.

4. Somatotropic hormone (STH) - increases sulfation during the biosynthesis of chondroitin sulfate.

5. Parotin is a specific hormone of the salivary glands. Reduces the level of Ca^{2+} in the blood, increasing its supply to the tissues, which is a favorable factor for the mineralization of teeth and bone tissue.

2. TASKS FOR INDEPENDENT WORK.

In the table with test tasks, underline the key words, choose the correct answer and justify it:

1.	In the child, the formation of enamel and dentin of the teeth is disturbed due to a decrease in the amount of calcium ions in the blood. Deficiency of which hormone can cause such changes? A. Thyrocalcitonin B. Parathyroid hormone C. Thyroxine D. Somatotropic hormone E. Triiodothyronine	
2.	The content of Ca^{2+} ions in the blood of the patient decreased sharply. This will lead to an increase in the secretion of which hormone? A. Parathyroid hormone B. Somatotropin C. Calcitonin D. Aldosterone E. Vasopressin	
3		

	Destruction of tooth enamel and dentine in vitamin C deficiency is largely due to impaired collagen maturation. What stage of procollagen modification is disrupted in this case? A. Hydroxylation of proline B. Glycosylation of hydroxylysine residues C. Formation of polypeptide chains D. Removal of C-terminal peptide from procollagen E. Cleavage of the N-terminal peptide	
4.	A patient suffering from chronic renal failure developed osteoporosis. Violation of the synthesis in the kidneys of which regulator of mineral metabolism is the cause of osteoporosis? A. Formation of $1.25(OH)_2D_3$ B. Hydroxylation of lysine C. Hydroxylation of proline D. Hydroxylation of cortisol E. Carboxylation of glutamate	
5.	In a child of the first year of life, a preventive examination revealed a violation of bone mineralization.	

	An insufficient amount of which vitamin can cause this? A. Folic acid B. Tocopherol C. Calciferol D. Cobalamin E. Riboflavin	
6	With osteolaterism, the strength of collagen decreases, due to a significant decrease in the formation of cross-links in collagen fibrils. The reason for this phenomenon is a decrease in the activity of such an enzyme: A. Collagenases B. Prolyl hydroxylases S. Lysyl oxidase D. Monoamine oxidases E. Lysyl hydroxylases	
7	In economically developed countries, dental caries is the most common disease. This disease affects more than 95% of the population. The main participation in the demineralization of the hard tissues of the tooth is attributed to: A. Malnutrition B. Metabolic regulation disorder S. Extreme effects on the body	

	D. Organic acids E. Deficiencies of vitamin C	
8	Name the calcium-binding protein of enamel, whose dysfunction plays an important role in the mechanism of enamel destruction in caries: A. Amelogenin B. Osteocalcin C. Parotyn D. Calcitonin E. Calmodulin	
9	Which of the following tooth tissues contains the least amount of water? A. Dentin. B. Enamel. C. Bones. D. Periodontics. E. Pulp.	
10	Dental disease fluorosis is associated with an excess of which element in food and water? A. Potassium. B. Calcium. C. Sodium D. Phosphorus. E. Fluoride.	

11	Which of the following mineral substances is contained in the hard tissues of the tooth in large quantities? A. Hydroxyapatite $[Ca_{10}(PO_4)_6(OH)_2]$. B. Carbonatapatite $[Ca_{10}(PO_4)_5CO_3]$. C. Chloropatite $[Ca_{10}(PO_4)_6Cl_2]$. D. Calcium phosphate $[Ca_{10}(PO_4)_6]$. E. Fluorapatite $[Ca_{10}(PO_4)_6F_2]$.	
12	Which trace element has the most pronounced cariogenic effect? A. Barium. B. Iron. C. Copper. D. Selenium. E. Strontium.	
13	The main methods of increasing enamel resistance include fluoridation. The mechanism of anti-caries effect of fluoride is related to: A. Synthesis of hydroxyapatite. B. Demineralization of the tooth.	

	C. Synthesis of the organic matrix of the tooth. D. Chlorapatite synthesis. E. Synthesis of fluorapatite.	
14	The child has a violation of the processes of ossification and "mottling of the enamel". The exchange of which trace element is disturbed? A. Iron. B. Copper. C. Zinc. D. Chromium. E. Fluoride.	
15	Enamel is characterized by high resistance to the influence of various mechanical and chemical factors. The synthesis of which component provides such resistance? A. Hydroxyapatite. B. Carbonate apatite. C. Collagen. D. Chlorapatite. E. Fluorapatite.	
16		

	The child complains of a toothache. The dentist diagnosed carious damage to the enamel. The amount of which mineral substances decreases in the area of carious damage: A. Potassium, phosphorus, fluorine. B. Sodium, calcium, potassium. C. Magnesium, fluorine, calcium. D. Phosphorus, magnesium, potassium. E. Phosphorus, fluorine, calcium.	
17	A woman, an employee of a confectionery shop, turned to a dentist. The patient drew attention to increased sensitivity to caries. For the purpose of remineralizing therapy, the doctor prescribed fluoride preparations. What is the role of fluoride in this therapy? A. Activation of salivary proteases. B. Increased enamel permeability. C. Reduction of proteoglycan synthesis. D. Increase in the formation of fluorapatite. E. Suppression of alcoholic fermentation.	

18	A decisive role in the process of tooth tissue calcification is played by the protein osteocalcin, which has a high ability to bind calcium ions, due to the presence of modified amino acid residues in the polypeptide chain: A. Alanine. B. Gamma-aminobutyric acid. C. Gamma-carboxyglutamine. D. Delta-aminopropionic acid. E. Carboxyasparagine.	
19	For the formation of the mineral matrix of the hard tissues of the tooth, a high concentration of phosphate ions is required, which are formed in the process of hydrolysis of phosphoroester bonds with the participation of alkaline phosphatase. Which metal ions are activators of this process: A. Calcium. B. Magnesium. C. Sodium. D. Iron. E. Zinc.	
20	A 10-year-old child lives in an area where the fluoride content in the	

	water exceeds the permissible norm. During the examination by a dentist, damage to the teeth in the form of chalk-like, as well as pigment spots and streaks was revealed. What is the most likely diagnosis? A. Erosion of teeth. B. Acid necrosis of hard dental tissues. C. Wedge-shaped defects. D. Medium caries. E. Fluorosis.	
21	A 35-year-old man came to the dentist with complaints of a decrease in the density of tooth tissue, increased tooth fragility when eating solid food. The Ca/P ratio in the enamel during scraping was determined in the laboratory. What value of this indicator indicates the strengthening of demineralization? A. 0.9. B. 1.7. C. 1.9. D. 2.5. E. 1.5.	
23		

	During the examination of a group of people living in the same territory, the dentist noticed the same symptoms of the disease - dark yellow stains on the enamel of the teeth. An excess of which trace element in food or drinking water can cause this condition? A. Iodine. B. Calcium. C. Copper. D. Nickel. E. Fluoride.	

3. <u>LITERATURE. Look page 320.</u>

LESSON №10

10. TOPIC: BIOCHEMICAL COMPOSITION AND FUNCTIONS OF BIOLOGICAL FLUIDS OF THE ORAL CAVITY IN NORMAL AND IN VARIOUS PATHOLOGICAL CONDITIONS

1. INFORMATION MATERIAL.

Saliva is an extracellular (transcellular) body fluid and is one of the fluids of the gastrointestinal tract. It is a transparent, viscous liquid that contains a mixture of substances. It is secreted by the salivary glands, and once it gets from the salivary glands to the oral cavity, it performs the following functions:

1. Mineralization - participates in the formation of enamel apatites.

2. Protective - saliva moisturizes and cleans the tissues of the oral cavity, supports the species composition of the microflora of the oral cavity, forms a protective barrier of mucin (gives it a viscous, mucous character) and other glandular proteins, leukocytes. Bere is absorbed into the formed pellicles of the teeth, prevents precipitation of a supersaturated solution of phosphate calcium from saliva.

3. Digestive – saliva moistens food, envelops food particles with mucin, facilitates swallowing, dissolves salts, sugars, and breaks down poly- and oligosaccharides.

4. Regulatory - regulates the formation of digestive juices in the gastrointestinal tract, the release of hormones and hormonoids that regulate the processes of tooth enamel mineralization and homeostasis of the oral cavity.

5. Excretory - together with saliva, low-molecular nitrogen-containing compounds (urea), cations and anions, metabolites of hormones, xenobiotics are secreted.

At a high rate of salivation, the pH reaches 7.8. When acidity shifts to the acidic side, especially at values of 6.0-6.2, there is focal demineralization of enamel with subsequent development of caries. When shifting into an alkaline environment, increased tartar formation occurs.

Normally, saliva has a slightly alkaline reaction (pH = 7,08 - 7,36). Mixed saliva contains organic and inorganic components (tab. 10.1).

Table 10.1

Biochemical composition of oral

Component	**Unit of measurement**
Dense substances	1,4–1,5 %
Organic substances	1 %
Precipitate	70 mg/l
Secretion	0.4 ml/min
Chlorides	2.5–3.0 g/l
Calcium ions	40–50 mg/l
Phosphates	190–200 mg/l
Fluorine	0.06–1.8 mg/l
Residual nitrogen	100–200 mg/l
pH	6,4–7,3
Protein	2–3 g/l
Protein fractions (electrophoresis) in %: — albumins; — α-globulins; — β-globulins; — γ-globulins; - lysozyme Lactic acid Pyruvic acid	 7–8 11–12 45 18 18–20 33 mg/l 9 mg/l
Mucin	3 g/l
Glycoprotein carbohydrates:— hexosaminase; — fucose;	 100 mg/l 90 mg/l

Component	Unit of measurement
— neuraminic acid; — common hexoses	12 mg/l 195 mg/l
Glucose	10–100 mg/l
Amylase	380 mg/l
Immunoglobulin A	190 mg/l
Immunoglobulin G	14 mg/l
Immunoglobulin M	2 mg/l
Urea	200 mg/l
Cholesterol	80 mg/l
Rhodanides (thiocyanates)	

Rhodanides are formed from hydrocyanic acid (the catalyst is rhodanese). In smokers, the level of thiocyanates in saliva is usually 4-6 times higher.

Regulation and mechanisms of saliva secretion. Forms of impaired salivation

It is known that the amount of saliva secreted per day depends on the characteristics of nutrition, moreover, there is no spontaneous secretion by the salivary glands. Secretion of saliva in the oral cavity can be unstimulated and stimulated.

Unstimulated is called saliva, which is formed in the absence of external factors that activate its formation. The rate of its secretion is on average 0.3-0.5 ml/min, and depends on daily and seasonal fluctuations. The peak of unstimulated secretion is in the middle of the day, and at night the secretion decreases to 0.05-0.1 ml/min.

Stimulated saliva released under the influence of external, artificial mechanical and (or) chemical factors. The rate of its secretion ranges from 0.8–7 ml/min (on average 1.5–2.3 ml/min)

Biochemical aspects of salivation

The metabolic processes that ensure saliva secretion in the cells of the acini of the salivary glands (SZ) are characterized by high intensity, which exceeds similar processes in hepatocytes and is somewhat inferior to them in kidney cells.

Energy generation is carried out in the process of glycolysis (in reactions of substrate phosphorylation) and in LPE (in the course of oxidative phosphorylation). Substrates for obtaining energy are mainly glucose and amino acids, which enter acinus cells from plasma in constant concentrations. The energy supply of the process of saliva secretion from acinus cells to the excretory ducts is provided by the hydrolysis of ATP under the action of Na^+/K^+-ATP-ase, which ensures the maintenance of the Na^+ electrochemical gradient.

The formed energy fund of acinus cells provides: the synthesis of peptides and proteins specific for the SZ, including enzymes and substances that determine the blood group, as well as their transport along the endoplasmic reticulum mesh and secretion into the excretory ducts; binding of the secretory component (SC) synthesized in the acini with the diameter of IgA1 with the formation of the secretory IgA2 molecule (IgAs) and secretion of the latter into the excretory ducts; selective transport of ions from plasma into primary saliva and selective secretion of ions and heavy metals. At the same time, acinus cells that do not use ATP provide transport and secretion of non-electrolyte organic compounds (albumins, globulins, immunoglobulins (G, M, A1)), proteinase inhibitors, amino acids, urea.

The functional relationship of the salivary glands with the main endocrine glands has been established in experimental and clinical trials. This is shown in relation to the hormones of the pituitary gland, pancreas, adrenal glands, gonads, gastrointestinal hormones.

One of the reasons for this connection is the presence of many hormones in saliva. The synthesis and secretion of many protein components of saliva is under the control of various blood substances.

Some sources indicate not only the content of sex hormones and thyroid hormones in saliva, but also the presence of nerve growth factors, epidermis, renin, and tonin.

The rate of saliva secretion is on average 0.3-0.5 ml/min; during sleep it decreases to 0.05 ml/min, and under the influence of irritants it increases to 1.5-2.3 ml/min. After eating sweets, the level of lactate in saliva increases, which indicates the activity of anaerobic glycolysis.

Biologically active substances of salivary glands

Nerve growth factor (NEGF) is a protein synthesized in the submandibular salivary gland (also in the placenta in humans) in the form of an inactive complex containing Zn^{2+}. NEGF is excreted in saliva and blood. The target cells for this hormone are:

1) neurons of the peripheral department of the sympathetic nervous system;

2) chromaffin cells of the adrenal glands;

3) sensory neurons of the spinal cord; 4) cholinergic neurons of the central nervous system;

4) fibroblasts**.**

The biological effects of NEGF are expressed in:

a) stimulation of neuron growth and mitosis of fibroblasts;

b) ensuring the survival of neurons;

c) protection of neurons from carcinogens;

d) differentiation of nerve cells with the subsequent transformation of neuroblasts into neurons, which is accompanied by an increase in the synthesis of neurotransmitters.

The release of NEGF into the oral cavity stimulates the healing of damaged tissues of the oral cavity. The biological effects of NEGF are a consequence of the effect on the metabolic processes of cells. K^+/Na^+-ATPase is activated in them. This leads to the accumulation of K^+ and the excretion of Na^+, the aerobic breakdown of glucose, the exchange of polyunsaturated fatty acids (PUFA) and

glycerophospholipids is stimulated. The formation of phosphoinositols is accompanied by an increase in the amount of intracellular calcium. NEGF increases the activity of ornithine decarboxylase with the subsequent synthesis of polyamines. In turn, polyamines stimulate the synthesis of nucleic acids and proteins. The synthesis and release of NEGF is regulated by neurotransmitters and hormones. Cholinomimetics, androgens and thyroxine increase the amount of NEGF. A similar effect is observed during pregnancy and lactation.

Epithelial growth factor (EGF) – a protein produced in the submandibular glands, as well as in the Brunner cells of the duodenum, pituitary gland, thyroid gland, and gastric mucosa. EGF is a polymer and consists of 2 subunits with Mg = 6 kDa and 2 subunits. Biological effects of EGF:

1) early eruption of incisors;

2) early opening of the eyelids;

3) proliferation and keratinization of the epithelium;

4) inhibition of hydrochloric acid secretion;

5) healing of stomach and duodenal ulcers;

6) vascular neoplasms.

EGF floats on the cells of the ectoderm: skin keranocytes, epithelial cells of the mucous membrane of the oral cavity, pharynx, esophagus, cornea, eye, mammary gland, lung alveoli, as well as mesoderm: chondrocytes, vascular epithelium. Mechanism of action EGF on cells is associated with a change in the permeability of the plasma membrane, which leads to the retention of Na^+ in the cell. It was established that there is a certain correlation between the accumulation of Na^+ in the cell and mitotic activity; with an increase in the concentration of 3`,5`-cGMP in the cell; with accelerated breakdown of glycerophospholipids and release of phosphoinositols and PUFAs. Released PUFAs are converted into prostaglandins and other compounds by the cyclooxygenase pathway. EGF also affects mineralized tissues. It acts similarly to parathyroid hormone and increases bone tissue resorption. EGF stimulates the division of odontoblasts and increases their DNA synthesis. However, EGF suppresses the differentiation of odontoblasts, which is accompanied

by a decrease in the synthesis of type I collagen, while its maturation slows down and the activity of alkaline phosphatase decreases. The formation of EGF increases androgens, thyroxine and progesterone. In case of increased production of EGF tumor transformation of cells is stimulated.

Parotin – a specific hormone secreted by the salivary glands, a protein. The active effect of parotin is associated with a glycoprotein that affects mesenchymal tissues: cartilage, tubular bones, tooth dentin. Parotin increases the proliferation of cartilage, stimulates the synthesis of nucleic acids and protein in odontoblasts, the mineralization of dentin and bones, and reduces the content of calcium and glucose in the blood plasma. Parotin also affects the spermatogenic epithelium and salivary gland epithelium, stimulating protein synthesis in these cells. Hyposalvation occurs when parotid gland secretion is disturbed

Kallikrein – glycoprotein. Causes limited proteolysis of globular proteins of kininogens with the formation of biologically active peptides-kinins: kalidin and bradykinin. Kinins are inactivated by kininases of the epithelial cells of the mucous membrane of the oral cavity. Kinins cause expansion of the vessels of the salivary glands and mucous membranes, which causes hyperemia, increased permeability of blood vessels, lowering blood pressure (hypotensive effect). Kallikrein exerts its effect in the ducts of the salivary glands, on the mucous membranes of the oral cavity, and in blood vessels when it enters the blood from the salivary glands.

Mucins – glycoproteins containing acidic polysaccharides. They give saliva a viscous character, and perform the role of mechanical protection of the mucous membrane of the mouth.

Renin – proteinase The biological effect of renin is related to the regulation of vascular tone and microcirculation, which in turn affects the processes of repair of the mucous membrane of the oral cavity and salivation. Renin too reveals a pressor effect associated with emotional stress and aggression. Lack of saliva leads to **xerotomy**, excessive secretion of saliva has a name **sialorrhea.** The rate of secretion is affected by food consumption and its nature, biorhythms, blood plasma

composition, hormonal status, salivary gland diseases, systemic diseases. One of the causes of xerotomy can be a lack of vitA.

Reduced speed noted in newborns, with acidosis, uremia, diabetes, dehydration, febrile conditions, menopause, systemic damage to the salivary glands - Sjögren's disease. In addition, the rate of secretion decreases under the influence of adrenaline, norepinephrine, dopamine.

Saliva secretion increases under the influence of acetylcholine, pilocarpine, bradykinin, nicotine, narcotic substances: morphine, cocaine. An increased rate of secretion was found during pregnancy, eruption of milk teeth, hyperacidic conditions, duodenal ulcer, under the influence of acidic and sweet irritants, chewing gum or paraffin, inflammatory processes of the mucous membrane of the oral cavity.

The use of taste stimuli leads to the formation of stimulated saliva. Acidic irritants and experimental chewing stimulate the separation of liquid saliva from the peri-auricular SZ. Under the influence of sucrose, the secretion of thick saliva from the submandibular, sublingual and small salivary glands increases.

Gingival fluid

This is the liquid content of the gingival groove. It represents a physiological environment of complex content. It contains leukocytes, epithelium, microorganisms, electrolytes, proteins, enzymes, etc. 0.5-2.5 ml of gingival fluid (GFL) enters the oral cavity per day.

In the mechanism of formation of gingival fluid, the morphological features of the structure of vessels and epithelium of the gingival canal are of great importance. The own layer of the mucous groove does not have papillae, and the border between the epithelium and the underlying tissues is represented by a straight line. The terminal vessels in this area are under the epithelium and parallel to it. This creates favorable conditions for transudation of capillary contents to the oral cavity, including even some blood proteins. The possibility of reverse flow of some molecules from the oral cavity is also shown.

Thus, in people with healthy periodontium (periodontal tissues), the gingival fluid is a serum transudate. Therefore, the content of minerals in gingival fluid is the same as

in blood plasma. The microbial composition of gingival fluid is similar to that of dental plaque. Many enzymes characteristic of blood and mucosal epithelium were isolated from gingival fluid. An important feature is that leukocytes enter the oral cavity through the jugular groove. This is the main point of entry of leukocytes into the oral cavity. Therefore, gingival fluid should be considered as an important part of antimicrobial protection. Mechanical removal of particles from the gingival canal with the help of gingival fluid prevents the possibility of stone formation in this area.

When periodontal disease is affected, gingival fluid is formed due to osmotic exudation, an increase in the level of amino acids is observed. As a result of the accumulation of products of bacterial metabolism and components of dental plaque, inflammatory changes occur, which cause serious disorders in the oral cavity. In addition, they can be the cause of the development of autoimmune processes with subsequent disruption of the connective tissue of the teeth. Such conditions are usually difficult to treat.

The gingival fluid includes:

Leukocytes – most of the leukocytes in the GFL (95-97%) are represented by neutrophils, 2% by lymphocytes and 2-3% by monocytes. During inflammation of the periodontium, the number of leukocytes increases.

Cocoa microflora - with the development of inflammation in the gums, the composition of the microflora of the gingival fluid changes, while spirochetes, fusobacteria, and protozoa appear instead of Gr(+) cocci.

In addition to leukocytes and bacteria, the GFL contains exfoliated epithelial cells, the number of which can increase during inflammatory processes.

Microelements Na^+ and K^+- with inflammation of the periodontium, the ratio of Na^+ and K^+ in the gingival fluid may change, while the amount of sodium and potassium may increase. In general, the destruction of periodontal tissues is often accompanied by an increase in the number of potassium ions. The gingival fluid also contains calcium, phosphorus, magnesium, zinc, sulfur, fluorine, and chlorine.

Proteins (albumins, globulins) – the amount of protein in hygge fluid is 61-68 g/l. It does not change with the development of periodontitis and does not depend

on the degree of severity of inflammation and oral hygiene. A change in the amount of protein will be associated with the active growth of pathogenic microflora in the oral cavity. Ig is secreted - a protein of the parotid gland that forms the local immunity of the mucous membrane.

Enzymes (various proteinases) – these enzymes play a special role in the destruction of cellular elements of the periodontium and the development of inflammation. First of all, these processes are associated with the activity of collagenase, which is not normally detected in gingival fluid. Its activity increases with periodontitis.

Enzymes play a leading role in the protection of the oral cavity and the initial stage of digestion.

α-Amylase - secretion of the parotid glands. It cleaves α (1,4)-glycosidic bonds in starch and glycogen.

Lysozyme - synthesized by the epithelial cells of the ducts of the salivary glands, cleaves the glycosidic bond in the murein polysaccharide chain. The destruction of the bacterial cell wall occurs - this is the antibacterial effect.

Carbonic anhydrase - synthesized in the acinar cells of the parotid and submandibular salivary glands. It accelerates the splitting of the C-O bond in the carbon cell and regulates the buffer capacity of saliva.

Peroxidases (ex. Catalase) oxidize thiocyanates, which suppresses the growth and metabolism of lactobacilli. A decrease in the activity of these enzymes is indicated by an increase in the formation of peroxides.

Cystatins participate in the formation of acquired tooth pellicle. Leukocytes are the source of nucleases. RNAases and DNAases slow down the growth and reproduction of many microorganisms in the oral cavity. High activity of alkaline and acid phosphatase also indicates inflammation of the soft tissues of the oral cavity.

Low-molecular and organic - normally their number is very small or absent, but increases sharply with inflammation of the periodontal tissues. Such substances

as hydrogen sulfide, indole, butyric, propionic and formic acids are synthesized by actively growing pathogenic microflora.

Glucose, hexosamines, uronic acids, cyclic nucleotides, urea, prostaglandins, phospholipids and triacylglycerols are also determined in the gingival fluid. The presence of urea and ammonia in the GFL maintains a high pH level of the GFL (from 6.3 to 7.93). However, the pH of GFL does not depend on the degree of inflammation. An increase in the level of glucose in the gingival fluid may indicate the development of diabetes. Excessive concentration of glucose in the oral cavity leads to the development of caries.

2. TASKS FOR INDEPENDENT WORK.

In the table with test tasks, underline the key words, choose the correct answer and justify it:

1.	Hyposalivation is observed in a patient with chronic inflammation of the submandibular salivary gland. Violation of the secretion of which substance is observed in this case? A. Glucagon B. Calcitonin C. Parotid gland D. Paratyrin E. Somatostatin	
2.	With age, the activity of the parotid salivary glands decreases. The activity of which enzyme decreases in saliva? A. Phosphatases B. Amylases	

	C. Hexokinase D. Maltase E. Lysozyme	
3.	What substance gives saliva a viscous mucous character, performs a protective role, in particular, against mechanical damage to the mucous membrane of the mouth? A. Lysozyme D. Amylase C. Kallikrein D. Glucose E. Mucin	
4.	A periodontist needs to evaluate the factors of non-specific resistance of saliva and oral fluid. What factor should be studied in the researched material in the first place? A. Complement B. Lysozyme C. Interferon D. Secretory IgA E. Properdin	
5.	The normal pH of saliva is 6.4-7.8. What changes in enamel will lead to a shift in the pH of saliva to the acidic side?	

	A. Calcifications B. Mineralization C. Demineralization D. Increasing stability E. Fluorosis	
6.	When eating cookies, candies, the lactate level in the mixed saliva temporarily increases. Activation of which biochemical process leads to this? A. Glycogenolysis B. Starch hydrolysis C. Gluconeogenesis D. Aerobic glycolysis E. Anaerobic glycolysis	
7.	During the examination of the patient's oral cavity, the dentist determined dryness of the mucous membrane and numerous erosions. The lack of which vitamin caused this phenomenon? A. A B. R C. S D. RR E. K	
8.	Periodontitis is accompanied by activation of proteolysis in periodontal tissues. An increase in which	

	components of oral fluid indicates its activation? A. Biogenic amines B. Amino acids C. Cholesterol D. Glucose E. Organic acids	
9.	To accelerate the healing of the wound of the mucous membrane of the oral cavity, the patient is prescribed a drug - a thermostable protein that is found in human saliva, tears, and breast milk. It is a factor of the body's natural resistance and is called: A. Imanin B. Complement C. Interleukin D. Interferon E. Lysozyme	
10	The child has been diagnosed with acute kidney failure. What biochemical indicators of saliva can be used to confirm this? A. An increase in α-amylase. B. An increase in immunoglobulin A. C. A decrease in alkaline phosphatase. D. By reducing the level of phosphate.	

	E. Increasing the level of residual nitrogen.	
11	What substance in the composition of saliva is synthesized in the salivary glands and outside them and gives saliva a thick and mucous character? A. Amylase. B. Maltase. C. Mucin. D. Sulfates. E. Phosphates.	
12	The normal pH of saliva is 6.4 - 7.8. A pH shift towards the alkaline side (7.8) creates conditions for: A. Enamel demineralization. B. Release of calcium from tooth tissue. C. Output of phosphorus from tooth tissue. D. Decreased resistance of tooth tissue to the action of cariogenic factors. E. Enamel mineralization.	
13	An excessive concentration of glucose in the oral fluid in diabetes leads to the development of: A. Enamel hyperplasia. B. Enamel hypoplasia. C. Multiple caries.	

	D. Enhanced enamel calcification. E. Fluorosis.	
14	One of the functions of saliva is protective, which is implemented, in particular, by the formation of local immunity of the mucous membrane due to the release of protein by the parotid gland: A. Albumin. B. Elastin. C. Collagen. D. Secretory immunoglobulin A. E. Fibrinogen.	
15	What substance gives saliva a viscous, mucous character, performs a protective role, protects the mucous membrane of the oral cavity from mechanical damage? A. Amylase. B. Glucose. C. Kallikrein. D. Lysozyme. E. Mucin.	
16	Which component of the oral fluid significantly increases the frequency of dental caries in diabetes? A. Ammonia.	

	B. Amino acids. C. Glucose. D. Residual nitrogen. E. Urea.	
17	Analysis of the saliva of a patient with periodontitis indicated a decrease in catalase activity. Activation of which process is noted in this patient? A. Anaerobic oxidation. B. Microsomal oxidation. C. Mitochondrial oxidation. D. Substrate phosphorylation. E. Formation of peroxides. (Free radical oxidation)	
18	Patient K. has reduced amylase activity in saliva. What pathology does this indicate? A. Hyperfunction of the parotid gland. B. Hypofunction of the parotid gland. C. Hypofunction of the submandibular gland. D. Hyperfunction of the hypoglossal gland. E. Hypofunction of the hypoglossal gland.	
19	It is known that the saliva of smokers has significantly more rhodanides than that	

	of non-smokers. This is related to the intake of what acids from tobacco smoke? A. Nitrogenous. B. Lemon. C. Nicotynova. D. Ottova. E. Synilna.	
20	The child has been diagnosed with acute kidney failure. What biochemical indicator of saliva can be used to confirm this? A. By increasing the content of free fatty acids. B. A decrease in the content of nucleic acids. C. An increase in the glucose content of saliva. D. A decrease in glucose content in saliva. E. An increase in the content of urea in saliva.	
21	Some saliva proteins perform a protective function. Indicate which of them protects the mucous membrane of the oral cavity from mechanical damage? A. Mucin. B. Lysozyme.	

	C. Catalase. D. Peroxidase. E. Renin.	
22	Based on the results of the analysis of the patient's saliva, it was established that the pH is 8.0, i.e. shifted to the alkaline side. This state of saliva contributes to: A. Development of tooth tissue hyperplasia. B. Development of tooth tissue hypoplasia. C. Development of caries. D. Development of fluorosis. E. Formation of tartar.	

3. <u>LITERATURE. Look page 320.</u>

LESSON № 11

11. TOPIC: BIOCHEMICAL FUNCTIONS OF THE LIVER. BIOTRANSFORMATION OF XENOBIOTICS. MICROSOMAL OXIDATION

1. INFORMATION MATERIAL.

The liver is the largest of the parenchymal organs. It performs a number of key functions:

1) it receives and distributes substances entering the body from the digestive tract, which are delivered by blood through the portal vein. These substances penetrate into hepatocytes, undergo chemical transformations, and in the form of intermediate or final metabolites enter the bloodstream and are carried to all organs and tissues;

2) serves as a place of bile formation;

3) synthesizes substances used in other tissues;

4) inactivates exogenous and endogenous toxic substances, as well as hormones.

The role of the liver in carbohydrate metabolism

The liver plays a leading role in maintaining physiological blood glucose concentration. The liver extracts most of the glucose from the intestines and uses it up: 10-15% of this amount for glycogen synthesis, 60% for oxidative breakdown, and 30% for fatty acid synthesis.

In physiologic hypoglycemia, glycogen breakdown is activated in the liver by glycogen phosphorylase. The resulting glucose-6-phosphate can be consumed in three ways:

1) by glycolysis with the formation of pyruvic acid and lactate;

2) by pentose phosphate metabolism;

3) breakdown by phosphatase to form glucose and phosphoric acid.

The last pathway prevails, leading to the release of free glucose into the general bloodstream.

Gluconeogenesis is actively taking place in the liver, in which the precursors of glucose are pyruvate and alanine (coming from muscles), glycerol from adipose tissue and a number of glucogenic amino acids from food. Excessive intake of glucose from food increases the intensity of all pathways of its transformation in the hepatocyte, including its oxidation with the formation of pyruvate. Its further breakdown requires a large amount of CoA, which is also used for the oxidation of fatty acids. As a result, the oxidation of fatty acids in the liver and the mobilization of lipids from fat depots slows down.

Lipid metabolism

The liver plays a leading role in the regulation of lipid metabolism.

The liver synthesizes bile acids, which, if deficient, impede the digestion and absorption of fats.

The liver produces and utilizes transport forms of lipids - lipoproteins.

With a deficiency of the main energy material - glucose, the liver activates the oxidation of fatty acids. In conditions of excess glucose, hepatocytes synthesize triacylglycerols and phospholipids from fatty acids that enter the liver from the intestines and are synthesized from glucose.

The liver plays a leading role in the regulation of cholesterol metabolism. The starting substance in its synthesis is acetyl-CoA. Excessive nutrition stimulates the formation of cholesterol, because the availability of the starting substrate for the synthesis of cholesterol - acetyl-CoA - increases (as a result of eating food containing carbohydrates and fats, because acetyl-CoA is formed during the breakdown of glucose and fatty acids).

In addition, the liver synthesizes ketone bodies, in particular acetoacetate and hydroxybutyric acid, which are carried by the blood throughout the body. The heart muscle and the adrenal cortex prefer to use these compounds as a source of energy rather than glucose.

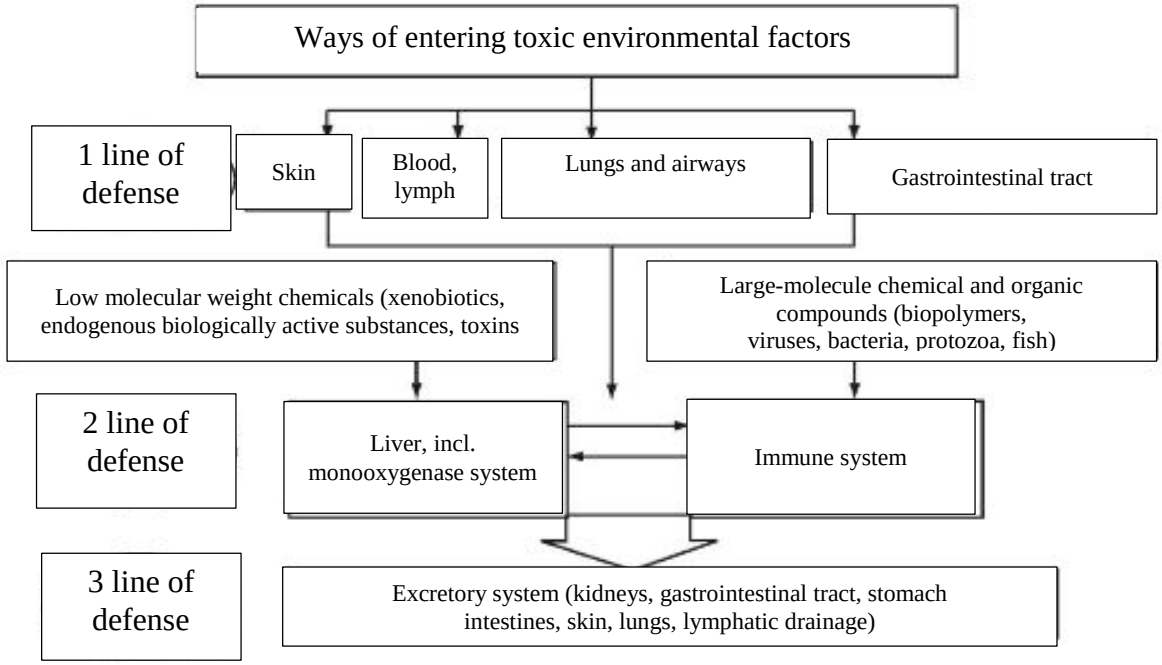
Metabolism of proteins

The liver uses amino acids from the digestive tract to synthesize its own proteins, but most of them are used to synthesize blood plasma proteins. The liver synthesizes fibrinogen, albumin (the normal level in blood plasma is 40-50 g/l), α- and β-globulins, and apolipoproteins.

The liver plays a central role in the metabolism of amino acids, as it actively carries out the processes of their chemical modification. In addition, it is in the liver that urea is synthesized.

The neutralizing function of the liver

In the current conditions of existence, the human body adapts to the toxic effects of foreign substances (xenobiotics) by using barrier mechanisms formed in the course of evolution.



Sources of xenobiotics for the human body can be very diverse: herbicides, insecticides used in agriculture; pollutants released into the environment by industrial enterprises; medicines, etc. When protein digestion is impaired in the human gastrointestinal tract, pathogenic intestinal microflora is activated, using undigested proteins and amino acids not absorbed in the small intestine for its growth and reproduction. In the human large intestine, as a result of metabolism in a

bacterial cell, amino acids can be converted into products that are toxic to humans when decarboxylated: for example, tyrosine to phenol, tryptophan to indole, or ornithine to putrescine. This process is called protein putrefaction in the large intestine. The resulting toxic decay products subsequently enter the bloodstream and can cause endotoxemia.

Biotransformation (neutralization) of non-polar lipophilic xenobiotics and endogenous toxic substances

The processes of biotransformation of xenobiotics and some endogenous metabolites are carried out mainly by liver enzyme systems localized mainly in the membranes of the smooth endoplasmic reticulum (ER) of hepatocytes. This allows us to consider the endoplasmic reticulum of hepatocytes as a metabolic barrier that plays an important role in protecting the internal environment of the body.

During differential centrifugation, the EPR defragments, turning into small bubbles called the microsomal fraction. Therefore, the reactions catalyzed by enzymes of EPR membranes are called microsomal, and the corresponding enzymes are called microsomal oxygenases. The essence of microsomal oxidation reactions is the hydroxylation of a substance using one atom of an oxygen molecule, the second atom combines with hydrogen atoms to form water. The hydrogen donor is reduced $NADPH+H^+$. Thus, the structure of the original substance changes, and thus its properties, both physicochemical - polarity increases - and biological - they can either inhibit or enhance. Hydroxylation allows the neutralization process to proceed to the second phase - conjugation reactions, during which other molecules of endogenous origin will be attached to the created functional group.

The main enzyme of the monooxygenase system, cytochrome P-450 (fig. 11.1), belongs to the family of flavin-dependent heme-containing proteins. To date, many isoforms of this enzyme have been identified and assigned to several families, depending on their properties and functions. In mammals, 13 subfamilies of cytochrome P-450 have been identified; enzymes of families I-IV are involved in the biotransformation of xenobiotics, while others metabolize endogenous

compounds (for example, steroid hormones androgens and corticosteroids are inactivated by enzymes of the liver microsomal oxidation system to 17-ketosteroids).

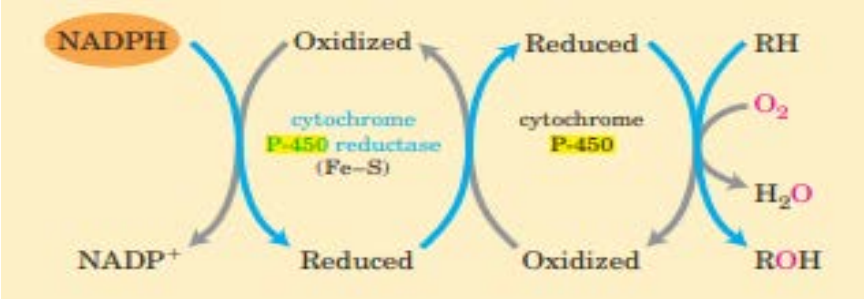


Fig. 11.1. The general scheme of the monooxygenase system

An important property of cytochrome P-450 and some other enzymes of the xenobiotic and endogenous toxin neutralization system is the ability to induce. For example, barbiturates, which are used in medical practice, have this induction property. Thus, the activity of neutralizing toxic substances in children is significantly lower than in adults due to the low activity of UDP-glucuronyltransferase. This enzyme catalyzes conjugation reactions of toxic compounds, in particular, bilirubin with glucuronic acid. In the case of low UDP-glucuronyl transferase activity, bilirubin accumulates in the blood of newborns and jaundice develops. To accelerate the maturation of microsomal enzyme systems in the liver of newborns, barbiturates (phenobarbital, luminal) are prescribed as inducers of enzymes of the toxic substance neutralization system. On the other hand, the inducibility of enzymes can lead to an addictive effect of certain drugs. The most common cause of "addiction" is the induction of liver enzymes by drugs and the acceleration of its own metabolism. This mechanism prevails in the development of addiction to barbiturates (phenobarbital, etc.).

The first stage of biotransformation involves the formation or release of hydroxy, carboxyl, thiol and amino groups, which are hydrophilic, and the molecule can be further transformed and excreted from the body. $NADPH+H^+$ is used as a coenzyme - a donor of reducing equivalents. In addition to cytochrome P-450,

cytochrome P450 reductase, cytochrome b5 reductase, and cytochrome b5 are involved in the first stage of biotransformation.

It should be borne in mind that many medicinal substances, once in the body, are converted into active forms at the first stage of biotransformation and have the necessary therapeutic effect. However, xenobiotics are often not detoxified, but rather toxified with the participation of the monooxygenase system and become more reactive.

The metabolic products of foreign substances formed at the first stage of biotransformation are subjected to further detoxification through a series of second-stage reactions. The compounds formed in this process are easily removed from the cells. The conjugation process catalyzed by glutathione S-transferase, sulfotransferase or UDP-glucuronyltransferase is preferred. Conjugation with glutathione, which leads to the formation of mercapturic acid, is generally considered to be the main mechanism of detoxification.

A clinically important example of a conjugation reaction is the formation of hypuroic acid when the amino acid glycine interacts with benzoic acid. Determination of the amount of hypuuric acid in the urine after a patient has taken a sodium benzoate solution is the basis for the study of antitoxic liver function (Quick test).

Conjugates with glutathione, glucuronic, sulfuric, acetic acids (for example, both hydroxyl and carboxyl groups of salicylic acid and its derivatives are conjugated with the acetyl group) and other substances are excreted mainly in the urine.

Thus, the metabolic chain of neutralization of hydrophobic toxic substances of external and internal origin in the liver includes the process of their conversion into hydrophilic compounds by oxidation and conjugation for further excretion.

Neutralization of reactive oxygen species

Molecular oxygen is not toxic to cells, but the products of its incomplete oxidation are dangerous: peroxide compounds, superoxide radicals, singlet oxygen,

etc. Due to their biological activity, these compounds are called reactive oxygen species (ROS). The appearance of ROS is caused by the fact that molecular oxygen (O_2) can intercept electrons from some carriers of the electron transport chain. As a result of the one-electron reduction of an oxygen molecule, a superoxide radical or anion radical O_2- is formed. A superoxide radical is a charged particle surrounded by water molecules. Therefore, O2- cannot cross the membrane, is "locked" in the cell and becomes a source of other forms of ROS, such as hydrogen peroxide: **O_2- + ě + $2H^+$ → H_2O_2.** Hydrogen peroxide, in turn, is reduced by superoxide and gives rise to a free hydroxyl radical: **H_2O_2 + O_2- → He- + He- + O_2**. The reactivity of the latter is extremely high, so a hydroxyl radical can oxidize almost any substance in the cell. ROS cause the formation of organic hydroperoxides (ROOH) of DNA, proteins, and lipids. This process is called peroxidation.

Cell protection is provided by the antioxidant system. The main way to protect against ROS is to inactivate them. This is achieved by the work of special enzymes: superoxide dismutase, catalase and peroxidase.

Superoxide dismutase (SOD) is an enzyme that is widespread in nature. The active center of SOD contains metal ions (copper, iron, manganese, zinc). SOD is present in all aerobic organisms and serves to effectively remove superoxide radicals. SOD catalyzes the conversion of two anionic radicals into hydrogen peroxide (H_2O_2) and molecular oxygen: **$2O_2$- + $2H^+$ → H_2O_2 + O_2**. Then catalase breaks down hydrogen peroxide to form water and molecular oxygen, and peroxidases reduce peroxide to water with special substrates, such as glutathione. Thus, catalase and glutathione peroxidase are the main primary antioxidants in the system of protection against the harmful effects of reactive oxygen species.

Glutathione plays a special role due to its ability to reduce hydrogen peroxide, ROOH hydroperoxides, and neutralize secondary metabolites. Glutathione is a γ-glutamylcysteinylglycine tripeptide containing a reactive thiol group. Most of it is in the reduced form (GSH) and plays a central role in the inactivation of toxic and reactive products. Oxidized glutathione is reduced by the enzyme glutathione reductase, using NADPH as a coenzyme. Glutathione performs a coenzyme function

in various enzymes. In addition to the previously mentioned glutathione S-transferase, it is used as a coenzyme by glutathione peroxidase (the active site also contains selenium). This enzyme catalyzes reactions in which hydrogen peroxide is reduced to water and organic hydroperoxides (ROOH) are reduced to hydroxy derivatives. Thus, proteins, lipids, and nucleic acids are protected from oxidative attack.

Although the role of catalase and glutathione peroxidase in the reduction of H_2O_2 in the liver is approximately the same, the activity of glutathione peroxidase is much more important for the cell as a whole. For example, catalase is localized mainly in peroxisomes, while glutathione peroxidase neutralizes hydrogen peroxide in the cytoplasm and mitochondria. The affinity of glutathione peroxidase for H_2O_2 is higher, so glutathione peroxidase protects against low concentrations of H_2O_2, which occur more often. In some tissues, for example, in the heart, catalase is almost absent, and therefore glutathione peroxidase plays a major role there. However, in the blood, catalase activity is high and this feature is used in clinical diagnosis. The analysis of blood catalase activity is used as a biomarker of metabolic disorders in the body. The activity of blood catalase can be observed during the treatment of bleeding wounds with hydrogen peroxide solution: when the solution enters the wound, abundant foaming occurs due to oxygen gas bubbles ($H_2O_2 + H_2O_2 = O_2 + 2H_2O$) and, as a result, mechanical cleaning of the wound from contaminating particles, small foreign bodies, and blood clots. This foaming promotes thrombosis and stops bleeding from small vessels. In case of hereditary catalase deficiency, foaming does not occur during rinsing with peroxide solution.

The liver, being the central metabolic organ, is involved in maintaining metabolic homeostasis and is able to interact with the reactions of protein, lipid and carbohydrate metabolism. In addition, the liver performs many other important functions: antitoxic, hematopoietic, etc. Therefore, the assessment of the functional state of the liver is an essential part of clinical and laboratory research. The number of existing liver function tests is extremely large. The main ones are: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase,

gamma glutamyl transpeptidase (GGT), albumin, cholinesterase (CHE), prothrombin index, etc.

2. TASKS FOR INDEPENDENT WORK.

In the table with the test tasks, underline the keywords, select the correct answer and justify it:

1.	In a patient undergoing a course of therapeutic fasting, normal blood glucose levels are maintained mainly by gluconeogenesis. From which amino acid is glucose most actively synthesized in the human liver? A. Lysine B. Alanine C. Glutamic acid D. Leucine E. Valine	
2.	A dry cleaning worker was diagnosed with fatty liver. Disruption of the synthesis of which substance in the liver can lead to this pathology? A. Cholic acid B. Phosphatidylcholine C. Tristearin D. Phosphatidic acid E. Urea	
3.	The patient's blood albumin concentration is 28 g/l, the concentration of lactate	

	dehydrogenase isoenzyme LDH5 is increased. What is the disease of which organ? A. Lungs B. Spleen C. Heart D. Kidneys E. Liver	
4.	A 4-year-old child was admitted to the clinic with signs of prolonged protein starvation: growth retardation, anemia, edema, mental retardation. The reason for the development of edema in this child is a decrease in liver synthesis: A. Lipoproteins B. Albumin C. Globulins D. Hemoglobin E. Glycoproteins	
5.	A patient with signs of acute alcohol poisoning was delivered to the clinic. What changes in carbohydrate metabolism are characteristic of this condition? A. The rate of gluconeogenesis decreases in the liver B. Aerobic glucose breakdown prevails in muscles	

	C. In the liver increases gluconeogenesis D. Anaerobic decomposition of glucose predominates in muscles E. In the liver increases the decomposition of glycogen	
6.	Detoxification of natural metabolites and xenobiotics is impaired in the patient's liver. The activity of which cytochrome can be reduced? A. Hemoglobin B. Cytochrome P-450 C. Cytochrome b D. Cytochrome oxidase E. Cytochrome c1	
7.	The patient came to the emergency room because of suppuration of the cut wound. To clean the wound from purulent discharge, the doctor washed it with 3% hydrogen peroxide solution. However, no foam was formed. What is the reason for the lack of effect of the drug? A. Hereditary catalase deficiency B. Presence of purulent contents in the wound C. Low concentration of H_2O_2 D. Shallow wound	

	E. Hereditary deficiency of erythrocyte phosphate dehydrogenase	
8.	In the process of metabolism in the human body, reactive oxygen species are formed, including superoxide anion radical. What enzyme inactivates this anion? A. Peroxidase B. Superoxide dismutase C. Glutathione peroxidase D. Catalases E. Glutathione reductase	
9.	A 55-year-old man was brought to the intensive care unit unconscious. According to relatives, it became known that he mistakenly drank an alcohol solution of an unknown manufacturer. According to the examination, he was diagnosed with methyl alcohol poisoning. What antidote should be used in this case? A. Acetylcysteine B. Teturam C. Ethanol D. Naloxone E. Protamine sulfate	

3. LITERATURE. See page 320.

LESSON №12

12. TOPIC: BIOCHEMISTRY OF MUSCLE AND CONNECTIVE TISSUE

1. INFORMATION MATERIAL.

Chemical composition of muscle tissue. Skeletal muscle contains 75-80% water and 20-25% dry matter. 85% of the dry residue is made up of proteins; the remaining 15% consists of various nitrogen-containing and nitrogen-free extractives, phosphorus compounds, lipoids, and mineral salts.

Muscle proteins. Sarcoplasmic proteins make up about 30% of all muscle proteins. Until recently, they were divided into two fractions - myogen, which is obtained from crushed muscle with water, and "globulin X", which is obtained with a 0.1 M KCl solution. However, new research shows that both of these fractions are not individual proteins, but are a mixture of different proteins. The bulk of sarcoplasmic proteins are enzymes, including glycolysis enzymes and a number of others. Muscle fibril proteins, unlike sarcoplasmic proteins, are extracted from muscles with stronger saline solutions (0.6 M KCl solution) and account for about 40% of the total muscle protein. This includes, first of all, the two most important proteins - myosin and actin.

Myosin is a globulin-type protein with a molecular weight of about 420,000. It contains a lot of glutamic acid, lysine, and leucine. In addition, along with other amino acids, it contains cysteine, and therefore has free -SH groups. Myosin molecules have a filamentous (fibrillar) structure. It is the most important component of the contractile complex and at the same time has enzymatic (adenosine triphosphatase) activity, catalyzing the breakdown of adenosine triphosphoric acid (ATP) into ADP and orthophosphate: $ATP = ADP + H_3PO_4$.

Actin has a much lower molecular weight (75,000) and can exist in two forms - globular (G-actin) and fibrillar (F-actin), which can change into each other. The molecules of the former have a rounded shape, while the molecules of the latter, which is a polymer (a combination of several molecules) of G-actin, have a filamentous shape. The transition of one form of actin to another is facilitated by

many ions, in particular K^+ and Mg^{2+}. G-actin has a low viscosity, while F-actin has a high viscosity. During muscle activity, G-actin is converted to F-actin. The latter easily combines with myosin to form a complex called actomyosin, which is the contractile substrate of the muscle that is capable of performing mechanical work. In muscle fibrils, actin is represented by thin filaments of "disk I" that extend into the upper and lower thirds of "disk A," where actin is probably connected to myosin.

The proteins of sarcosomes (mitochondria) and microsomes are mainly enzyme proteins. In particular, sarcosomes contain enzymes of aerobic oxidation and respiratory phosphorylation. Proteins of muscle fiber nuclei are nucleoproteins containing deoxyribonucleic acids in their molecules.

Muscle fiber stromal proteins, which make up about 20% of the total muscle protein, are highly insoluble and cannot be extracted from the muscle by saline. The sarcolemma is constructed from stromal proteins - myostromins.

Muscle extractives. Skeletal muscle contains a large amount of non-protein substances that easily pass from the crushed muscle into an aqueous solution after protein precipitation.

Nitrogen-containing extractables include, first of all, creatine, which makes up 0.35 to 0.6% of muscle weight, the dipeptides anserine and carnosine, glutamine, and glutamic acid. Muscles contain some free amino acids, urea, uric acid, adenine, guanine, hypoxanthine, and xanthine in small amounts.

The most important of the nitrogen-free extractables is the reserve carbohydrate, glycogen, which is partially free in the sarcoplasm and partially bound to proteins. Its content in muscles varies widely (from 0.2 to 2% of muscle weight), depending on the body's fatness and the degree of its training. In trained muscles, the glycogen content is twice as high as in untrained muscles. During fasting, the glycogen content decreases dramatically.

Nitrogen-free muscle extractives also include intermediate products of carbohydrate breakdown - hexose phosphorus esters (primarily glucose-6-phosphate and fructose-6-phosphate), pyruvic and lactic acids. Very small amounts of fatty acid

oxidation products, such as β-oxybutyric and acetoacetic acids (so-called "ketone bodies"), may also be present.

Muscle phosphorus compounds. About 80% of the phosphorus compounds found in muscles are water-soluble. This includes the main source of energy for muscle contractions - adenosine triphosphoric acid (ATP) and creatine phosphate, which is used for ATP resynthesis. In resting muscles, ATP is in a bound state, probably in the form of a complex compound with myosin. Under the influence of training, the content of creatine phosphate increases. ATP and creatine phosphate make up the bulk of the water-soluble phosphorus compounds found in muscle. The latter also include the aforementioned hexose phosphorus esters and some other phosphorylated metabolic intermediates, as well as various coenzymes such as codihydrogenase, cocarboxylase, etc. Phosphorus compounds insoluble in water are phospholipids.

Muscle lipids. Muscle fibers contain up to 1% of protoplasmic fat associated with sarcoplasmic protein structures. It is not consumed during muscle work and during fasting. Muscles capable of prolonged work contain more phospholipids. In addition, muscles contain cholesterol.

Minerals. Minerals (ash residue after muscle burning) make up 1-1.5% of muscle weight. This includes mainly PO_4^- and Cl^- anions and cations Na^+, K^+, Ca^{2+}, Mg^{2+}, etc.

According to the chemical composition of mammalian muscles according to Zbarovsky, 72-80% of the muscle mass is water. Most of the dry residue (16-21%) is made up of proteins, and the rest is organic matter and mineral salts.

Each muscle consists of several thousand muscle fibers, united by connective tissue layers and the same membrane. The muscle is a multicomponent complex. Muscle fibers are built of longitudinally arranged myofibrils, about 1 micron in diameter, in which you can see how dark and light disks alternate. Dark disks have double birefringence and are called A- (anisotropic) disks; light disks that do not have double birefringence are called I- (isotropic) disks. In the middle of the I disk there is a dense Z line that permeates the entire fiber, as if holding the myofibrils in

a bundle and, at the same time, organizing the location of the A- and I-disks of many myofibrils. A bundle of myofibrils from one Z-line to another is called a sarcomere. Each sarcomere includes:

1) a network of transverse tubes oriented at a 90% angle to the longitudinal axis of the fiber, which connect to the outer surface of the cell;

2) sarcoplasmic reticulum, which makes up 8-10% of the cell volume;

3) several mitochondria.

Myofibrillar structures are aggregates consisting of thick filaments with a diameter of about 14 nm and thin filaments with a diameter of 7-8 nm located between them. The filaments are arranged in such a way that the thin ones enter the gaps between the thick ones with their ends. The thick filaments are composed of the protein myosin (fig. 12.1).

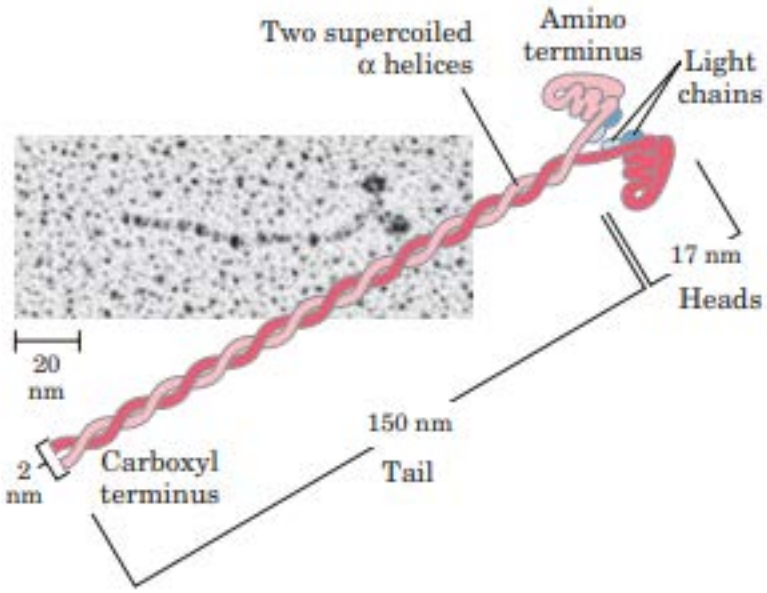


Fig. 12.1. Myosin structure

Myosin molecules combine to form filaments, consisting of approximately 400 rod-shaped molecules linked to each other in such a way that pairs of myosin molecule heads lie at a distance of 14.3 nm from each other; they are arranged in a spiral.

Thin filaments consist of actin, tropomyosin, and troponin.

Actin is a water-soluble globular protein with a molecular weight of 42 kDa; this form of actin is referred to as G-actin. In muscle fibers, actin is found in a polymerized form, which is referred to as F-actin. Thin muscle filaments are formed by double-stranded actin structures interconnected by non-covalent bonds.

Tropomyosin - is a rod-shaped molecule consisting of two different α-helical polypeptide chains twisted relative to each other. This molecule is located in the groove of the F-actin helical chain.

Troponin - (Tn) is a spherical molecule consisting of three different subunits, which are named according to their functions: tropomyosin-binding (Tn-T), inhibitory (Tn-I) and calcium-binding (Tn-C). Each component of the thin filaments is connected to two other non-covalent bonds.

In the muscle, where all the components discussed above are assembled together in a thin filament, tropomyosin blocks the attachment of the myosin head to the adjacent F-actin monomer. Calcium, binding to Tn-C, significantly changes the conformation of the protein, increasing the degree of interaction between troponin subunits and simultaneously weakening the bond between Tn-I and F-actin. This leads to the movement of the tropomyosin molecule along the groove of the thin filament. The result of this movement is the opening of the myosin-binding center on the surface of actin.

The mechanism of muscle contraction, the role of calcium ions in the mechanism of muscle contraction.

Muscle contraction is initiated by the arrival of an action potential at the motor nerve ending plate, where the neurohormone acetylcholine is located, whose function is to transmit impulses. Initially, acetylcholine interacts with acetylcholine receptors, which leads to the propagation of the action potential along the sarcolemma. All this causes changes in the permeability of the sarcolemma to Na^+ cations, which are directed into the muscle fiber, neutralizing the negative charge on the inner surface of the sarcolemma. The sarcolemma is connected to the transverse tubes of the sarcoplasmic reticulum, to which the excitation wave propagates. From

the tubes, the excitation is transmitted to the membranes of vesicles and cisternae, which braid myofibrils in areas where actin and myosin filaments interact. When the signal is transmitted to the cisternae of the sarcoplasmic reticulum, the latter begin to release the Ca^{2+} they contain. The released Ca^{2+} cross-links with Tn-C, which causes conformational changes that are transmitted to tropomyosin and then to actin. Actin is released from the complex with thin filament components in which it was located. Next, actin interacts with myosin, and the result of this interaction is the formation of a junction, which makes it possible for thin filaments to move along thick ones. The generation of force (shortening) is determined by the nature of the interaction between myosin and actin. A movable hinge appears on the myosin rod, in the area of which a turn occurs when the globular head of myosin binds to a certain section of actin. It is these turns, occurring simultaneously in numerous sites of myosin-actin interaction, that cause the actin filaments (thin filaments) to be drawn into the H-zone. Here they come into contact (at maximum shortening).

The energy for this process is supplied by the hydrolysis of ATP. When ATP is attached to the head of the myosin molecule, where the active center of myosin ATPase is localized, a bond between the thin and thick filaments is not formed. Calcium cation neutralizes the negative charge of ATP, facilitating the rapprochement with the active site of myosin ATPase. As a result, myosin is phosphorylated, i.e., myosin is charged with energy, which is used to form a junction with actin and move the thin filament. After the thin filament has moved one "step", ADP and phosphoric acid are cleaved from the actomyosin complex. Then a new ATP molecule is attached to the myosin head and the whole process is repeated with the next myosin head. ATP consumption is also necessary for muscle relaxation. After the motor impulse is over, Ca^{2+} is transferred to the cisternae of the sarcoplasmic reticulum. Tn-C loses its associated calcium, resulting in conformational shifts in the troponin-tropomyosin complex, and Tn-I closes the active centers of actin again, making them unable to interact with myosin. The concentration of $Ca2^{+}$ in the contractile proteins becomes below the threshold and muscle fibers lose the ability to form actomyosin. Under these conditions, the elastic

forces of the stroma, deformed at the time of contraction, prevail and the muscle relaxes. At the same time, thin filaments are pulled out of the space between the thick filaments of the A disk, the H zone and the I disk acquire their original length, and the Z lines move away from each other to the same distance. The muscle becomes thinner and longer. The rate of ATP hydrolysis during muscle work is enormous: up to 10 mmol per 1 g of muscle per 1 minute. Total ATP reserves are small, so to ensure normal muscle function, ATP must be restored at the same rate as it is consumed.

ATP resynthesis during muscle activity can be carried out both in the course of reactions that take place in anaerobic conditions and due to oxidative transformations in cells associated with oxygen consumption.

Creatine kinase reaction. The first and fastest process of ATP resynthesis is the creatine kinase reaction. Creatine phosphate (CP) is a macroergic substance that, when ATP reserves in the working muscle are depleted, gives a phosphorylated group to ADP:

$$Kf + ADP \leftrightarrow K + ATP$$

This process is catalyzed by creatine kinase. The creatine kinase reaction plays a major role in the energy supply of short-term maximal power exercises.

Aerobic, anaerobic glycolysis. Enzymes that catalyze glycolysis reactions are localized on the membranes of the sarcoplasmic reticulum and in the sarcoplasm of muscle cells. Glycogen phosphorylases and hexokinase, enzymes of glycogenolysis and the first glycolysis reaction, are activated when the sarcoplasmic content of ADP and phosphoric acid increases.

The myokinase reaction occurs in the muscle with a significant increase in the concentration of ADP in the sarcoplasm, when the possibilities of other pathways are almost exhausted or close to it. The essence of this reaction is that the interaction of 2 molecules of ADP produces 1 molecule of ATP:

$$ADP + ADF\ ATP + AMP.$$

The conditions for the inclusion of the myokinase reaction occur with severe muscle fatigue. Therefore, the myokinase reaction should be considered an "emergency" mechanism.

Biochemical changes in muscles in pathologies

The main pathologies characteristic of muscle tissue are muscular dystrophy, atony and metabolic myopathies, which cause profound changes in the chemical composition and metabolism of muscles.

In ***dystrophy, a decrease in*** total muscle mass is observed as a result of a decrease in myofibrillar proteins and an increase in stromal proteins - collagen and elastin. In muscle cells, the glycogen content decreases and glycolysis is inhibited, and the synthesis of ATP and creatine phosphate is inhibited. Impaired synthesis of the latter increases the content of free ***creatine*** in the muscles and blood and increases its excretion in the *urine*. At the same time, the renal excretion of *creatinine decreases* sharply, which is explained by impaired synthesis of creatine phosphate, from which creatinine is formed. In muscular dystrophy, protein catabolism also increases, as evidenced by increased levels of *ammonia, glutamic acid and glutamine*. The content of carnosine and anserine is significantly reduced. One of the features of all types of muscular dystrophy (e.g., progressive Duchenne muscular dystrophy) is the release of specific muscle enzymes such as *creatine phosphokinase and aminotransferase into the* blood plasma, and their activity in the blood plasma increases significantly. Determination of *creatine phosphokinase* activity in the blood serum is the most informative test for the early diagnosis of muscular dystrophies.

In muscle ***atony, there is a*** lack of normal tone of skeletal muscles and internal organs, which develops as a result of malnutrition, nervous system disorders, infectious diseases, and endocrine gland disorders. In this pathology, the activity of ***creatine phosphokinase decreases in muscle*** tissue.

In case of ***mechanical*** damage to muscle tissue, the content of *creatine phosphokinase and* ***creatinine in the*** blood increases, and the excretion of the latter in the urine increases. These indicators are used to diagnose muscle injuries.

Biochemical changes in the myocardium in coronary heart disease

Coronary heart disease is one of the most common heart muscle pathologies. The pathogenesis of this disease is based on impaired oxygen supply to cardiomyocytes, which leads to a switch in heart muscle metabolism from aerobic to anaerobic. As a result of activation of anaerobic glycolysis, lactic acid is formed and acidosis occurs. Under these conditions, tissue respiration and associated ATP synthesis are inhibited. ATP deficiency reduces the activity of ion transport systems, resulting in an increase in the content of sodium ions in cardiomyocytes and a decrease in the content of potassium ions. Lack of ATP and discoordination of ion transport leads to irreversible changes in cardiomyocyte function, which causes ischemic necrosis - *myocardial infarction.*

For the *diagnosis* of myocardial infarction, it is important to study the activity of certain enzymes and their isoforms in the blood plasma.

The main markers of myocardial cell damage are enzymes such as *creatine phosphokinase* (CK, CF isoform), *aspartate aminotransferase* (AST), and lactate dehydrogenase isoenzymes (LDH_1 and LDH_2). The determination of CFK is used as the most specific test, and an increase in the activity of this isoenzyme is absolute proof of myocardial damage. An increase in LDH_1 activity within the first three days after the onset of pain also plays an important diagnostic role. The highest diagnostic value of LDH_1 elevation is in the first 16-20 hours of myocardial infarction, when the total LDH activity does not exceed the norm. LDH_1 may remain elevated even after total LDH has already returned to normal.

Biochemistry of connective tissue

Connective tissue is a complex of specialized cells, fibers and basic amorphous substance that forms the internal environment and integrates other cells

and tissues into a single multicellular human body. Connective tissue accounts for up to 50% of the human body weight.

The main functions of connective tissue are trophic, protective, supporting, plastic and morphogenetic.

Varieties of connective tissue differ in the composition and ratio of cells, fibers, as well as the physical and chemical properties of amorphous intercellular substance. Connective tissue is divided into three types:

1. Connective tissue itself:

- loose - there are few fibers, going in different directions. This tissue forms the soft skeleton of organs;

- dense unformed. This tissue forms the mesh layer of the skin;

- dense organized tissue.

2. Connective tissues with special properties:

- reticular - forms the stroma of blood vessels;

- adipose tissue - forms subcutaneous fatty tissue;

- pigmented - forms the iris of the eyes;

- mucous membrane is found only in the umbilical cord of the fetus;

- blood and lymph.

3. Skeletal tissues:

3.1. Bone - has special mechanical properties. It consists of osteocyte cells, which are of two types:

a. Osteoblasts - destructive cells that break down bone tissue and make room for calcium and nutrients;

b. osteoclasts - bring calcium and nutrients.

The intercellular substance consists of osseous fibers and mineral salts (calcium phosphate - $Ca_3(PO_4)_2$ - is the main building material for vertebrate bones and teeth). The function of bone tissue is support, protection, protein and mineral metabolism.

3.2. Cartilage - consists of chondrocyte cells. There are three types of cartilage tissue:

a. hyaline (vitreous) cartilage - forms the cartilage of the larynx and the surface of bone joints;

b. elastic cartilage - forms the auricle;

c. fibrous cartilage - forms intervertebral discs. The function of cartilage tissue is supporting and mechanical.

3.3 Cement and dentin of the tooth.

The main cells of connective tissue

The main cells of connective tissue are fibroblasts, macrophages, mast cells, adventitial cells, plasma cells, pericytes, fat cells, and leukocytes that migrate from the blood; sometimes pigment cells.

Macrophages are involved in the destruction of microorganisms, neutralization of toxic substances and produce immune bodies.

Fibroblasts are the main secretory cells involved in the formation of connective tissue. The main function of fibroblasts is the formation of basic substance and fibers (this is manifested in wound healing, scar tissue development, and the formation of a connective tissue capsule around a foreign body). In mature fibroblasts, the biosynthesis of collagen, elastin proteins, and proteoglycans is intensive. Fibroblasts are motile cells. Fibroblast movement is possible only after they bind to supporting structures with the help of fibronectin, a glycoprotein synthesized by fibroblasts and other cells that provide adhesion. Fibrocytes are the final forms of fibroblast development. The synthesis of collagen and other substances in these cells is reduced. Myofibroblasts combine the ability to synthesize not only collagen but also contractile proteins. In addition, fibroblasts produce components of the extracellular matrix - nidogen, laminin, tinascin, chondroitin-4-sulfate, proteoglycans. Fibroblasts that have completed the developmental cycle are called fibrocytes.

Fibroblast is a cell with high phagocytic and hydrolytic activity, which is involved in the "resorption" of intercellular substance during organ involution.

Scar formation occurs mainly due to the extracellular matrix, in particular with the help of collagen. The extracellular matrix is a supramolecular complex that includes chemical compounds of various types (proteins, polysaccharides, proteoglycans, etc.). It can be compared to a gel in which fibrous proteins (collagen and elastin) and viscous proteins (fibronectin, laminin) "float", providing the interconnection of molecules with each other and with cell surfaces. The growth of excess extracellular matrix in the scar occurs as a result of the activity of "wound" fibroblasts. In intact (healthy) skin, fibroblasts are responsible for the remodeling of dermal components, they destroy old collagen and deposit new collagen. In case of injuries, traumas, burns and surgical interventions, myofibroblasts appear in the wounds, seeking to "close the gap" in the tissues, intensively depositing components of the extracellular matrix: collagen, glycosaminoglycans, elastin and other proteins. It is due to the proliferation of fibroblasts and their production of excess extracellular matrix that scar healing occurs.

Mast cells are regulators of local connective tissue homeostasis; they are involved in reducing blood clotting, increasing the permeability of the blood-brain barrier, in the processes of inflammation and immunogenesis. Most mast cell granules contain heparin, chondroitin sulfates, hyaluronic acid, and histamine.

Histamine rapidly causes dilation of blood capillaries, increases their permeability, which is observed in localized edema. It has a pronounced antihypertensive effect and is an important mediator of inflammation.

Heparin reduces intercellular substance permeability and blood coagulation, has anti-inflammatory effect. It is synthesized in fatty cells, which are accumulated in animal organs, especially in the liver, lungs, and vascular walls. Histamine acts as its antagonist.

Adipocytes are capable of accumulating large amounts of reserve fat, which is necessary for trophism, energy production and water metabolism.

Adventitial cells accompany blood vessels.

Pericytes surround blood capillaries and are part of their walls.

Pigment cells contain the pigment melanin in their cytoplasm.

Connective tissue fibers

There are two types of fibrous structures in the intercellular matrix: collagen and elastin fibers.

Collagen fibers consist of several collagen bundles with a certain number of collagen fibrils. Collagen and albumin are isolated from the fibers.

Collagen is a complex protein, belongs to the group of glycoproteins. In humans, it makes up 30% of the protein mass and 70% of the skin protein mass. Collagen fibers are embedded in organs and are a complex structure inside and outside the pleura, pericardium, abdominal cavity and organs such as the heart, liver, lungs, kidneys, bones, blood vessels, eyeball, and skin.

Collagen is insoluble in water, saline solutions, and weak solutions of acids and alkalis. This is due to the peculiarities of its primary amino acid structure. Amino acids are arranged in groups (triads) with similar structures along the length of the polypeptide chain. Every third amino acid in the primary structure of collagen is glycine. Triad: (Gly-X-Y)n, where X is any amino acid or oxyproline, Y is any amino acid or oxyproline or oxylisin. The most commonly repeated combination in collagen is Gly-Pro-Op. These amino acids are repeated many times in the chain. Hydroxyproline guarantees the stability of collagen. The formation of transverse covalent bonds - "crosslinks" in collagen fibrils occurs under the action of the enzyme lysyl oxidase, which contains copper and the coenzyme pyridoxal phosphate. With a decrease in the activity of this enzyme, the strength of collagen decreases, which can cause the development of a number of diseases.

The secondary structure of collagen is also unusual: the pitch of one helix turn is less than three amino acids. Such a dense packing of the helix is explained by the presence of glycine. There are almost 30 types of collagen, which differ in molecular organization, organ and tissue affiliation.

The stimulating factors of collagen biosynthesis are copper, iron, chromium ions, and ascorbic acid. The enzyme collagenase breaks down immature collagen inside cells, thereby regulating the intensity of its secretion at the cellular level.

Collagen synthesis and maturation is a complex multi-stage process that begins in the cell and ends in the intercellular matrix. Collagen synthesis and maturation involve a number of post-translational changes:

a) hydroxylation of proline and lysine to form hydroxyproline (Hyp) and hydroxylisin (Hyl);

b) glycosylation of hydroxylysine;

c) partial proteolysis - cleavage of the "signal" peptide, as well as N- and C-terminal propeptides;

d) formation of a triple helix.

The formation of collagen fibers is a special type of multistage postribosomal processing of a protein molecule, each subsequent stage of which is possible only after the previous one is fully realized. Therefore, disruption of any of them leads to a variety of pathological processes. Individual collagen chains are synthesized on ribosomes, after which they are transferred to the endoplasmic reticulum as precursors of pro-α chains containing additional peptides at the N and C ends.

Hydroxylation of proline and lysine in the procollagen molecule occurs after the synthesis of the polypeptide chain is completed with the help of specific proline and lysine hydroxylases, cofactor of which is ascorbic acid. Glycosylation is provided by transglycosidases, the substrates of which are UDP-glucose and UDP-galactose. After secretion from the cells, procollagen fibers lose additional peptides, forming collagen molecules that combine into fibers. Mutations in the genes involved in the formation of different types of collagen at any stage lead to the development of collagen diseases.

As a result of collagen breakdown, free hydroxyproline appears in the blood and urine. Most of this amino acid is catabolized by the enzyme hydroxyproline oxidase, and some of it is excreted in the urine. Therefore, hydroxyproline is a marker amino acid that is used to judge the rate of collagen breakdown.

In some diseases associated with connective tissue damage, due to accelerated collagen breakdown, hydroxyproline excretion increases. This is observed in Paget's disease, hyperparathyroidism, collagenosis, and some infectious diseases. In case of

impaired hydroxyproline catabolism, which is usually caused by a defect in the hydroxyproline oxidase enzyme, hydroxyproline excretion may exceed 1 g/day.

Elastic connective tissue consists of thick, rounded, or flattened fibers that often branch. Elastic fibers are connective tissue elements that can lengthen as a result of hydration and return to their original length. Elastin is a polymer composed of tropoelastin monomers containing 850 amino acids, mainly valine, glycine and alanine. Elastin, due to its elasticity, allows many body tissues, especially the skin, to restore their shape after stretching or compression. Elastic fibers always branch, stretch and form the framework of large vessels, trachea, bronchi, etc.

Amorphous component of the intercellular substance

Cells and fibers of connective tissue are enclosed in the so-called amorphous component or basic substance. It is a gel-like substance that is a metabolic, integrative and buffering multicomponent environment surrounding cells and fibrous structures of connective tissue, nerve and vascular elements. The components of the basic substance include blood plasma proteins, water, inorganic ions, metabolic products of parenchymal cells, dissolved collagen and elastin precursors, proteoglycans, glycoproteins and complexes formed by them.

Proteoglycans (PGs) are protein-carbohydrate compounds containing 90-95% carbohydrates and 5% protein. The protein component is a special COR-protein to which glycosaminoglycans (GAGs) are covalently attached with the help of trisaccharides.

GAGs are polysaccharide compounds containing hexuronic acid with amino sugars (N-acetylglycosamine, N-acetylgalactosamine).

In the cell, GH are bound to hyaluronic acid. Chains of glycosaminoglycans in proteoglycans form macromolecular mesh structures and provide the function of a molecular sieve with certain pore sizes. GAG molecules contain many hydroxyl, carboxyl and sulfate groups that have a negative charge and easily attach water molecules and ions that determine the hydrophilic properties of tissues. GAGs are involved in the formation of fibrous structures of connective tissue and its

mechanical properties, in the reparative processes of connective tissue, in the regulation of cell growth and differentiation.

Among these compounds, hyaluronic acid is the most common in connective tissue types, as well as sulfated GAGs: chondroitin sulfates (in cartilage, skin, cornea), dermatan sulfate (in skin, tendons, blood vessel walls, etc.), keratan sulfates, heparan sulfates (in many basal membranes).

Hyaluronic acid is composed of repeating non-sulfated disaccharide units. It is a mucopolysaccharide containing acetylglucosamine and glucuronic acid. Hyaluronic acid has a high viscosity; its biological significance lies mainly in the fact that it is a cementing substance of connective tissue. Hyaluronic acid is a component of the skin; its high content in the extracellular matrix plays an important role in hydrodynamics and migration processes in tissues.

Hyaluronidase ("spreading factor"), contained in various tissues of the body, causes the breakdown of hyaluronic acid to glucosamine and glucuronic acid and thereby reduces its viscosity, increases tissue permeability and facilitates the movement of fluids in interstitial spaces.

The action of hyaluronidase is reversible. With a decrease in its concentration, the viscosity of hyaluronic acid is restored. Thus, hyaluronidase can be used to temporarily reduce the viscosity of hyaluronic acid.

The ratio of the hyaluronic acid-hyaluronidase system largely regulates tissue permeability. Increased activity of hyaluronidase and other mucolytic enzymes results in disorganization of connective tissue and depolymerization of its basic substance. The specific substrate of hyaluronidase is glycosaminoglycans (hyaluronic acid, chondroitin, chondroitin sulfate), which form the basis of the intercellular matrix of connective tissue. As a result of depolymerization under the action of hyaluronidase, glycosaminoglycans lose their viscosity, ability to bind water and metal ions. As a result, the formation of collagen fibers becomes more difficult, the permeability of tissue barriers increases, the movement of fluid in the intercellular space is facilitated, and tissue trophism improves. Clinical consequences of these processes include increased elasticity of connective tissue,

reduction of contractures and prevention of their formation, reduction of the adhesive process, scarring, and accelerated resorption of hematomas.

Keratins are a family of fibrillar proteins characterized by high mechanical strength. Keratins are the basis of the stratum corneum of the epidermis: skin, hair, and nails. Keratan sulfates are built from disaccharides. Keratan sulfate 1 and dermatan sulfate are found in the cornea, located between collagen fibers and are involved in its transparency.

Heparin consists of glucosamine and two types of uronic acids - glucuronic and iduronic. Most of the amino groups of glucosamine are sulfated, and a smaller part is acetylated. The protein part of proteoglycans is rich in amino acids such as serine and glycine. Heparin is an important anticoagulant. It binds to hemostatic factors IX, XI, but the most important is its interaction with antithrombin III. Heparin changes protein conformation, enhancing interaction with serine peptidases.

Sialic acids are monobasic polyoxyamino acids that are derivatives of neuraminic acid and are part of glycoproteins and glycolipids. Present in all tissues and fluids of the human body, they have strong acidic properties, so they are not normally found in the free state in the body.

The largest amount of sialic acids is found in human saliva, as well as in the secretions of the glands of the mucous membranes. Blood serum contains a small amount of sialic acids, which are also combined with proteins and some hormones, providing a longer circulation of these compounds in the bloodstream. The content of sialic acids is normally 620-730 mg/L of blood serum and fluctuates in a number of pathological conditions. A significant increase in their concentration occurs in diseases of inflammatory genesis (in particular, rheumatoid arthritis). The accumulation of free and bound sialic acids in the bloodstream (sialidosis) occurs as a result of a genetically determined defect in the sialidase enzyme, which is involved in the excretion of sialic acids from the body.

Chondroitin sulfates are connective tissue glycosaminoglycans. They are mainly part of cartilage, ensuring its strength and regulating water metabolism.

The pathology of glycosaminoglycans is a violation of their synthesis, breakdown, or both processes simultaneously. A number of pathological conditions, grouped under the name mucopolysaccharidoses, have been studied in the most detail. They are caused by a deficiency of enzymes necessary for the degradation of these oligosaccharides.

Systemic connective tissue diseases or diffuse connective tissue diseases are a group of diseases characterized by a systemic type of inflammation of various organs and systems, combined with the development of autoimmune and immunocomplex processes, as well as excessive fibrosis with a number of common clinical and pathological signs (fever, polyarthritis, myositis, myalgias, various internal organ injuries, lymphadenopathy, and CNS damage). These include systemic lupus erythematosus, systemic scleroderma, dermatomyositis, Sjögren's syndrome, rheumatoid arthritis, rheumatism, and rheumatic polyalgesia. Systemic connective tissue diseases are united by a common substrate - connective tissue - and a similar pathogenesis. The intercellular matrix, which is much larger than the cell mass, includes collagen, reticular, elastic fibers and the main substance consisting of proteoglycans. Therefore, the term "collagenosis" is outdated; the more correct name for the group is "systemic connective tissue diseases".

In collagen diseases, characteristic changes in the hyaluronic acid system, which is part of the main substance of connective tissue, are noted, leading to mucoid swelling, fibrinoid degeneration, hyalinosis and collagen necrosis. Signs such as vague polyarthralgic and myalgic syndrome, aggravated by various nonspecific factors, various skin rashes, asthenization (increased fatigue, decreased performance), subfebrile temperature, vague cardiac complaints, periodic appearance of protein in the urine, especially with a persistent increase in ESR and leukopenia, indicate the possibility of systemic lupus erythematosus. Reactions such as the determination of C-reactive protein, fibrinogen, sialic acid are often positive. The destruction of collagen fibers is accompanied by the release of the amino acids oxyproline and oxylisin, which are excreted in the urine.

In rheumatism, collagen fibers are affected, their destruction occurs under the influence of various toxins, while the collagen structure is disrupted, which contributes to the generalization of the rheumatic process. There is an increase in the activity of hyaluronidase, which leads to increased breakdown of hyaluronic acid and the release of amino sugars, including sialic acids, the level of which increases in the blood.

3. TASKS FOR INDEPENDENT WORK.

In the table with the test tasks, underline the keywords, select the correct answer and justify it:

1.	A 30-year-old woman had been ill for about a year when she first began to experience joint pain, swelling, and redness of the skin over them. The preliminary diagnosis was rheumatoid arthritis. One of the probable causes of this disease is a change in the structure of connective tissue protein: A. Myosin B. Mucin C. Collagen D. Troponin E. Ovoalbumin	
2.	Increased fragility of blood vessels, destruction of enamel and dentin of teeth in patients with scurvy is largely due to impaired collagen maturation. What stage of procollagen	

	modification is impaired in this vitamin deficiency? A. Removal of the C-terminal peptide from procollagen B. Glycosylation of hydroxylysine residues C. Cleavage of the N-terminal peptide D. Formation of polypeptide chains E. Hydroxylation of proline	
3.	In patients with collagenosis there is a process of destruction of connective tissue. This is confirmed by the increase in blood count: A. The content of creatine and creatinine B. The content of oxyproline and oxylizine C. Transaminase activity D. The content of urates E. Activity of LDH isozymes	
4.	Fibrillar elements of connective tissue include collagen, elastin and reticulin. Indicate the amino acid that is only a part of collagen and the determination of which in biological fluids is used to diagnose connective tissue diseases. A. Lysine	

	B. Proline C. Glycine D. Phenylalanine E. Hydroxyproline	
5.	A 63-year-old woman has signs of rheumatoid arthritis. An increase in the level of which of the following blood parameters will be most significant in confirming the diagnosis? A. Acid phosphatase B. Total glycosaminoglycans C. N-glycosidase D. Lipoproteins E. Total cholesterol	
6.	A patient with progressive muscular dystrophy was examined by biochemical examination of urine. The appearance of which substance in large quantities in the urine can confirm the disease of the muscles in this patient? A. Porphyrins B. Hypuric acid C. Urea D. Creatinine E. Creatine	
7.	A patient with a crush of muscle tissue was delivered to the	

	traumatology department. What biochemical indicator of urine will be increased? A. Mineral salts B. Glucose C. Common lipids D. Uric acid E. Creatinine	
8.	The study of the patient's blood revealed a significant increase in the activity of MB-forms of CK (creatine phosphokinase) and LDH-1. What is the most likely pathology? A. Myocardial infarction B. Pancreatitis C. Hepatitis D. Rheumatism E. Cholecystitis	
9.	The patient has muscle atony. Name the enzyme of muscle tissue, the activity of which can be reduced in this condition. A. γ-Glutamyltransferase B. Catalase C. Amylase D. Creatine phosphokinase E. Transketolase	
10.	A 47-year-old man was admitted to the intensive care unit with a	

	diagnosis of myocardial infarction. Which of the fractions of lactate dehydrogenase (LDH) will prevail in the blood serum during the first two days? A. LDH 3 B. LDH5 C. LDG 1 D. LDG4 E. LDH 2	
11.	As a result of exhausting muscle work, the buffering capacity of the blood has significantly decreased. This phenomenon can be explained by the entry of which acidic substance into the blood? A. Pyruvate B. Lactate C. 3-phosphoglycerate D. 1,3-bisphosphoglycerate E. α-ketoglutarate	
12.	In the patient's blood, an increase in the activity of LDH_1, LDH_2, ALT, creatine kinase was detected. In which organ of the patient is most likely to develop a pathological process? A. Pancreas B. Skeletal muscles	

	C. Liver D. Kidneys E. Heart	
13.	A 46-year-old patient has long been suffering from progressive muscular dystrophy (Duchenne). Changes in the level of which enzyme in the blood is a diagnostic test in this case? A. Glutamate dehydrogenase B. Lactate dehydrogenase C. Pyruvate dehydrogenase D. Creatine phosphokinase E. Adenylate cyclase	
14.	A 36-year-old patient suffers from collagenosis. An increase in the content of which metabolite is most likely to be found in the urine? A. Oxyproline B. Creatinine C. Urea D. Indacin E. Urobilinogen	
15.	A young man of 18 years old was diagnosed with muscular dystrophy. Increase in the serum content of which substance is most likely in this pathology? A. Myoglobin B. Alanine	

	C. Creatine	
	D. Myosin	
	E. Lactate	

3. LITERATURE. See page 320.

LESSON №13

13. TOPICS: BLOOD BIOCHEMISTRY, LIPOPROTEINS, ENZYMES, NON-PROTEIN COMPONENTS OF PLASMA

2. INFORMATION MATERIAL.

Blood is a tissue of the internal environment with a liquid intercellular substance (plasma) containing various cellular and extracellular elements. The total volume of blood in humans is 6-8% of their body weight (on average 4-6 liters). Up to 1 liter of blood is stored in depots, mainly in the spleen.

Blood functions:

1) **transport:** the most universal function associated with the transfer of various substances (gases, nutrients, hormones, etc.). For example, complex proteins low-density lipoprotein (LDL) and high-density lipoprotein (HDL) are involved in cholesterol transport;

2) **homeostatic:** ensuring the stability of the internal environment (acid-base, osmotic balance, water balance of tissue fluids);

3) **protective:** neutralization of antigens by specific and nonspecific mechanisms;

4) **excretory:** transport of end products of metabolism to the lungs, kidneys, skin, etc;

5) **respiratory:** transport of oxygen and carbon dioxide;

6) **nutritional (trophic):** transport of digestion products of proteins, lipids, and carbohydrates;

7) **regulation of body temperature** through the redistribution of heat with the blood flow.

Normally, blood, as a tissue, consists of plasma and the cellular elements contained in it. The latter include red blood cells, white blood cells, and platelets. Plasma accounts for about 55% of the blood volume.

Among the approximately 100 different protein components of blood, simple proteins are mainly represented by albumin and globulins. Complex proteins include

glycoproteins, lipoproteins, phosphoproteins, chromoproteins, metalloproteins, and nucleoproteins.

Plasma proteins can be separated into 5 fractions by electrophoresis: albumin (albumin, transthyretin), α_1-globulins (prothrombin, transcortin), α_2-globulins (ceruloplasmin, haptoglobin), β-globulins (fibrinogen, transferrin) and γ-globulins (immunoglobulins, interferon, fig. 13.1).

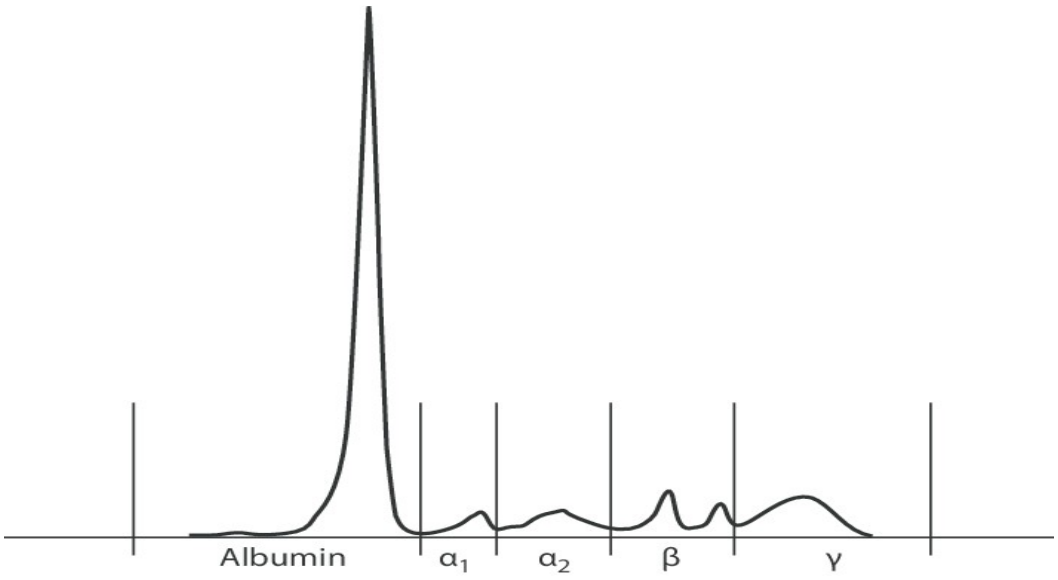


Fig. 13.1. Electrophoregram of serum proteins

For clinical and diagnostic purposes, the value of total protein in the blood serum is often investigated, which is normally 65-85 g/l. Abnormalities in the content of proteins in the blood plasma include **hyperproteinemia** (> 85 g/l), **hypoproteinemia** (<65 g/l), **paraproteinemia** (the appearance of proteins in the blood serum that are not normal), **dysproteinemia** (a change in the percentage of individual protein fractions with normal values of total serum protein).

Hyperproteinemia:

1. Hypersynthetic (true). It occurs as a result of hyperproduction of protein (e.g., Ig), paraproteins (e.g., in B-cell leukemia, plasmacytoma, myeloma);

2. Hemoconcentration (false). It develops as a result of hemoconcentration without increased proteosynthesis (for example, in burn disease, diarrhea, repeated vomiting, prolonged excessive sweating).

Hypoproteinemia:

1. Hyposynthetic (true), can be of two types:

a) primary (hereditary or congenital) - for example, hypoproteinemia in Bruton's disease;

b) secondary (acquired, symptomatic) - for example, in case of liver failure, protein starvation, renal failure, hypoaminoacidemia of various genesis, burn disease.

2. Hemodilution (false). It is caused by hypervolemia (for example, in hyperaldosteronism or renal failure).

Paraproteinemia is observed in:

a) myeloma: tumor plasmocytes produce abnormal light or heavy chains of the Ig molecule;

b) lymphomas (lymphocytic or plasmacytic): abnormal IgM is synthesized.

Acute phase proteins

In some diseases, there is a change in the ratio of protein fractions during electrophoresis, as well as a sharp increase in the concentration, or the appearance of acute phase proteins that are not typical for the normal state of the body: C-reactive protein, cryoglobulin, alpha-1-antitrypsin, serum amyloid A and P, orosomucoid, transferrin, ceruloplasmin, alpha-2-macroglobulin.

C-reactive protein is a very sensitive blood component that reacts most quickly to tissue damage. It is most commonly detected in rheumatic diseases, gastrointestinal diseases, cancer, myocardial infarction, neonatal sepsis, tuberculosis, meningitis, and postoperative complications.

Cryoglobulin is a protein that precipitates at low temperatures. It is most often determined in autoimmune diseases (systemic lupus erythematosus,

rheumatoid arthritis), vasculitis, viral hepatitis B and C, liver disease (biliary cirrhosis), kidney disease (glomerulonephritis), Raynaud's disease.

Ceruloplasmin (serum concentration of ceruloplasmin in adults is normally 180-450 mg/l) is a copper-containing protein, an increase in the concentration of which is caused by infectious diseases, especially in latent or chronic form. Also, an excess of ceruloplasmin is determined in the following pathological conditions: liver cirrhosis, hepatitis of various genesis, tremors, muscle tone disorders, the presence of Fleischer's rings (a brown stripe around the iris), growth retardation, jaundice, increased fatigue, difficulty swallowing, walking, anemia, etc.

Lipoproteins

An important clinical indicator in the human body is an increase in the level of lipoproteins (LP). All plasma lipoproteins have a core consisting of cholesterol esters and triacylglycerols. Chylomicrons and very low-density lipoproteins (VLDL) are formed in the intestine and liver, respectively, and high-density lipoproteins (HDL) are formed in the intestine, liver, and blood from other LDL. Some apoproteins have been identified, each of which has certain properties associated with the transformation of lipoproteins in the body. When chylomicrons and VLDL enter the bloodstream, they capture apoprotein C-II from HDL and activate membrane-bound lipoprotein lipase, catalyzing the cleavage of triacylglycerols in them. During the catabolism of acylglycerols, apoprotein C-II returns to HDL, and chylomicrons and VLDL are converted to low-density lipoprotein (LDL), the main source of cellular cholesterol. LDL enters all cells of the body, interacts with a special membrane receptor, the activity of which decreases with increasing intracellular cholesterol concentration. HDL, on the other hand, is able to remove cholesterol from cells and transport it to the liver. It is believed that high plasma levels of LDL and VLDL are an important factor in the development of atherosclerosis (a disease caused by deposits of cholesterol and its esters on the inner surface of blood vessels).

Non-protein nitrogenous components of blood

In clinical practice, great importance is attached to the determination of non-protein nitrogenous components of the blood: residual nitrogen and its constituent products. **Residual nitrogen** is the nitrogen of compounds that remain in the blood after the precipitation of its proteins. The normal content of residual nitrogen in the blood is 14.3-28.6 mmol/l. The latter includes a group of nitrogen-containing compounds (urea, amino acids, uric acid, creatinine, indica, etc.).

The main end product of protein metabolism in the body is **urea**. Normally, its concentration in the blood is 3.3-6.6 mmol/l. An increase in blood urea content is a sign of renal dysfunction. In acute renal failure, the concentration of urea in the blood reaches 50-83 mmol/l.

Important non-protein nitrogenous substances in the blood include **uric acid** (UA) and its salts. In humans, UA is the end product of purine base metabolism. Normally, the concentration of UA in the blood is 0.18-0.24 mmol/l (in blood serum - about 0.29 mmol/l). An increase in the content of SC in the blood (hyperuricemia) is the main symptom of gout. With gout, the level of SC in the blood serum rises to 0.5-1.1 mmol/l.

Creatinine is an important indicator of kidney function (normal blood level: women - 53-97 mmol/l, men - 62-115 mmol/l). Creatinine is the end product of creatine metabolism. Creatine is synthesized in the body, mainly in the kidneys and liver, from three amino acids - arginine, glycine and methionine (normal blood creatine levels: women - 13-53 mmol/l, men - 27-71 mmol/l). When phosphorylated, it is converted to creatine phosphate, which is the most important source of energy for muscle contraction. An increase in blood creatine may indicate an increased breakdown of muscle tissue.

Blood enzymes

The blood contains many enzymes and isozymes, but their amount is so minimal that they cannot be detected as a separate electrophoretic fraction. Blood enzymes are conventionally divided into three groups:

1. **Blood's own enzymes** (secretory) - enzymes that are synthesized in the liver and released into the plasma, perform certain functions in the blood. These are enzymes of the blood coagulation and anti-coagulation systems: lipoprotein lipase, triglyceride lipase, LCHAT, cholinesterase.

2. **Indicator enzymes** are enzymes that enter the bloodstream from tissues as a result of cell death or damage to their membranes and the release of enzymes into the bloodstream. For example, AST (aspartate aminotransferase), ALT (alanine aminotransferase), LDH (lactate dehydrogenase), CK (creatine phosphokinase), acid and alkaline phosphatase, etc.

3. **Excretory enzymes** are enzymes that are synthesized in the liver and normally excreted in bile. When bile outflow is impaired, their content and activity in plasma increases (alkaline phosphatase, leucine aminopeptidase).

In enzyme diagnostics, the activity of enzymes of all groups (secretory, indicator, excretory) is determined, but the most important is the determination of organ-specific indicator enzymes.

For example, in myocardial infarction, the activity of ALT, LDH-1, LDH-2, CK (MB isoenzyme) increases; in prostate adenoma, the level of acid phosphatase increases; in pancreatitis, lipase, amylase; in hepatitis, ALT, LDH-4, LDH-5.

Violation of the acid-base balance

Acid-base balance, acid-base balance of blood is a set of physicochemical and physiological processes that determine the relative stability of the hydrogen index (pH) of the internal environment of the body. Normally, the pH of human blood is maintained within the range of 7.35-7.47, despite the intake of acidic and basic metabolic products into the bloodstream. Stability of the pH of the internal environment of the body is a necessary condition for the normal course of life processes.

Acidosis (acidification) develops as a result of an increase in the concentration of H^+ ions or a decrease in the concentration of HCO_3^- ions, which leads to acidemia, i.e. a decrease in the pH of arterial blood below 7.35.

Distinguish:

1. **Metabolic acidosis**. This condition occurs as a result of excessive formation or intake of organic or inorganic acids in the body. Most often, the formation of acids increases due to metabolic disorders, such as diabetes mellitus or starvation, when an excess of products of incomplete oxidation of proteins, fats and carbohydrates, which are mainly acids, is created in the tissues and blood.

2. **Respiratory acidosis**. The cause of respiratory acidosis is a decrease in the excretion of carbon dioxide from the body through the lungs as a result of impaired function of the lung tissue itself, the innervating apparatus, respiratory muscles, decreased excitability of the respiratory center and other reasons.

Alkalosis (alkalization, alkalemia) occurs due to a decrease in the concentration of H^+ ions in body fluids or an excess of HCO_3^- ions, which leads to an increase in the pH of arterial blood over 7.45.

Distinguish:

1. **Metabolic alkalosis**. It occurs as a result of excessive loss of acids, especially chlorine, in the composition of HCl, and potassium from the extracellular fluid of the body (then hypokalemic, hypochloremic alkalosis occurs) or due to excessive intake of alkali metal salts - bicarbonates, etc.

2. **Respiratory alkalosis**. Respiratory alkalosis is caused by primary hyperventilation, which can occur as a result of direct stimulation of the respiratory center, brain damage, hysteria and salicylate poisoning.

Blood hemostasis system

The hemostasis system is a biological system that ensures, on the one hand, the preservation of blood in a liquid state, and, on the other hand, the prevention and control of bleeding.

Blood clotting (hemocoagulation) is a complex multi-stage enzymatic process in which, in addition to the primary (vascular platelet) link of hemostasis, the coagulation link is involved, which ensures the formation of a fibrin thrombus,

i.e., the final stop of bleeding. The coagulation link of hemostasis is represented by 3 systems: coagulation (procoagulants), anticoagulation (anticoagulants), plasma, or fibrinolytic, which provides lysis of a fibrin clot.

These systems, which are links in a single biological process, are in physiological balance, ensuring the body's homeostasis. The clotting mechanism can be summarized as follows. Under the influence of prothrombinase (prothrombin activator), which is formed during tissue damage, platelet aggregation and destruction, as well as as a result of complex chemical interactions of coagulation factors, plasma prothrombin is converted to thrombin, which, in turn, breaks down fibrinogen (a group of proteins that is an important part of coagulation homeostasis) dissolved in the plasma to form fibrin. Fibrin fibers form the basis of the thrombus, which is further stabilized by factor XIII. In a few hours, fibrin fibers are actively compressed - retraction (reduction) of the clot occurs. In the presence of various diseases or age-related characteristics of a person, the formation of a clot inside the vessel can lead to partial or complete blockage (thrombosis). These conditions are dangerous and, in some cases, not compatible with life. To prevent and treat this condition, drugs are used that affect different stages of coagulation. The most commonly used drugs are acetylsalicylic acid (aspirin), heparin, and streptokinase.

Heparin is a heteropolysaccharide (glucosaminoglycan) used in medical practice as an anticoagulant. The mechanism of action is due to its ability to bind specifically to antithrombin III, which dramatically increases the inhibitory effect of the latter on thrombin and other proteases involved in blood clotting.

Aspirin can block cyclooxygenase, which is involved in the synthesis of eicosanoids.

Streptokinase, combining with the blood protein plasminogen, forms a complex that activates the conversion of plasminogen to plasmin (fibrinolysin), an active proteolytic enzyme that dissolves fibrin fibers in blood clots. Plasmin destroys fibrinogen and other clotting factors, preventing clot formation. The drug dissolves blood clots both on their surface and from the inside.

The basic biochemical indicators of blood (norm) are shown in tables 13.1 - 13.7

Table 13.1

Plasma proteins

Indicator	Units	SI units
Total blood protein	6.5-8.5 g%	65-85 g/l
Albumins	4-5 g%	40-50 g/l
Globulins	2-3 g%	20-30 g/l
Fibrinogen	0.2-0.4 g%	2-4 g/l

Table 13.2

Protein fractions (electrophoretic activity)

	A. A. Pokrovsky (1969), rel. %	F. I. Komarov and others. (1982), rel. %	V. G. Kolb and others. (1976) (n = 100)		
			rel. %	g %	SI - g/l
Albumins	56.6-66.8	51-61.5	61.5±0.7	4.97±0.07	49.7±0.7
Globulins					
α_1	3-5,6	3.6-5.6	5.5±0.21	0.45±0.02	4.5±0.2
α_2	6.9-10.5	5.1-8.3	6.7±0.20	0.56±0.02	5.6±0.2
β	7.3-12.5	9-13	9.2±0.24	0.76±0.02	7.6±0.2
γ	12,8-19	15-22	16.8±0.34	1.39±0.03	13.9±0.3

Table 13.3

Basic blood amino acids

Amino acid	Contents		Amino acid	Contents	
	mg%	mmol/l		mg%	mmol/l
Glycolol	2.8-3.0		Arginine	1.6-3.0	91.8-172.2
Alanine	3.2-5.6	359.0-628.3	Lysine	2.1-5.3	143.9-363.1

Methionine	0.3-0.5	20.1-33.6	Glutamic acid	0.8-1.1	54.4-74.8
Valin	2.2-3.2	188.1-273.6	Glutamine	7.5-8.3	513.8-568.6
Leucine	1.7-3.3	129.7-251.8	Proline	2.6	222.2
Isoleucine	1.6-2.0	121.1-152.6	Serin	1.16	110.4
Tyrosine	1.4-1.5	77.3-82.8	Threonine	1.9-2.1	159.6-176.4
Phenylalanine	1.4-1.9	84.7-114.9	Histidine	1.7-2.1	109.7-135.5
Tryptophan	1.0	49.0	Cysteine	2.0-3.0	166.6-249.9

Table 13.4

Lipid components of blood plasma

Lipid fractions	**Contents**	
	units	**SI units**
Total lipids	350-800 mg %	4.6-10.4 mmol/l
Phospholipids	150-380 mg%	1.95-4.9 mmol/l
Lipid phosphorus	6.1-14.5 mg %	1.97-4.68 mmol/l
Neutral lipids	0-200 mg %	
Triglycerides (blood serum)	50-150 mg%	0.565-1.695 % mmol/l
Non-esterified fatty acids	20-50 mg %	0.71-1.75 mmol/l
Free fatty acids	0.3-0.8 meq/l	0.3-0.8 μmol/l
Total cholesterol	120-250 mg %	3.11-6.48 mmol/l
Free cholesterol	40-90 mg % (30-40% of the total)	1.04-2.33 mmol/l

Cholesterol esters	90-135 mg % (60-70% of the total)	2.33-3.49 mmol/l
Free cholesterol / cholesterol esters = 0.55 - 0.60		
α-Lipoproteins (25-30%) (high-density lipoproteins)	220 mg %	2.2 g/l
men	125-425 mg %	1.25-4.25 g/l
women	250-650 mg %	2.5-6.5 g/l
β-Lipoproteins (65-75%) (low density lipoproteins)	35-55 units optical density (turbidimetric method)	

Table 13.5

Residual nitrogen and its components

Indicator	Contents		% of nitrogen from all residual nitrogen	
	in mg/100 ml	SI units		
	In blood serum			
Residual nitrogen	20-40	7.06-14.1 mmol/l	100	
Urea	20-40	3.3-6.6 mmol/l	50 (46-60)	
Amino acid nitrogen	2.0-4.3	1.43-3.07 mmol/l	25	
Uric acid	2-6,4	0.12-0.38 mmol/l	4	
Creatine:				
men	0.2-0.7	13-53 mmol/l	5	7.5
women	0.4-0.9	27-71 mmol/l	2.5	
Creatinine:				
men	1-2	0.088-0.177 mmol/l		
women	0.5-1.6	0.044-0.141 mmol/l		
Ammonia	0.03-0.06	21.4-42.8		

Other non-protein substances (polypeptides, nucleotides, etc.)			13
Xanthoprotein reaction.	20 units		
Creatine: whole blood	3-4 mg %	229-305 mmol/l	
plasma	1-1.5 mg%	76.3-114.5 mmol/l	
Blood urea nitrogen (urea: 2.14)	9-14 mg %	3.18-4.94 mmol/l	

Table 13.6

Indicators of the acid-base state of the blood

Indicator	**SI units**
Hydrogen ion concentration (pH)	
men	7.36-7.42
women	7.37-7.42
Partial pressure of CO_2 (pCO_2):	
men	35.8-46.6 mm Hg. Art.
women	32.5-43.7 mm Hg. Art.
Buffer bases (BB)	44.9-51.9 meq/l of blood
Base excess (BE)	
men	2.4-2.3 meq/l of blood
women	3.3-1.2 meq/l of blood
Standard Bicarbonate (SB)	18.8-24.0 meq/l of plasma
True Bicarbonate (AB)	21.3-24.8 meq/l of plasma
Total CO_2	21-26 meq/l of plasma

Table 13.7

Activity of blood enzymes

Indicator	Units	SI units
α-amylase of blood plasma	12-32 mg of starch (mg/h)	12-32 g/(h.l)
Aspartateaminotransferase	8-40 units	0.1-0.45 mmol/(h·l)
Alanineaminotransferase	5-30 units	0.1-0.68 mmol/(h·l)
Lactatedehydrogenase general	0.8-4.0 μmol pyruvate / (ml·h)	0.8-4.0 mmol/(h·l)
Lactate dehydrogenase is urea unstable	25-36% of the total	
Cholinesterase	160-340 μm of acetic acid / (ml·h)	160-340 mmol/(h·l)
γ- Glutamyl transpeptidase		0.6-3.96 mmol/(h·l)
Lipase	0.28 IU/l	
General alkaline phosphatase	1-3 μmol of paranitrophenol/(ml-h)	1.0-3.0 mmol/(h·l)
General alkaline phosphatase	0.5-1.3 μmol of inorganic phosphorus (ml·h)	
Isoenzymes of LF	Up to 20% of the total	
General acid phosphatase	0.025-0.12 μmol of inorganic phosphorus (ml·h)	
Trypsin	1-4 μmol/(ml min)	60-240 μmol /(ml·h)
Fructose-1-phosphate aldolase	0-1 units	
Fructose-1,6-phosphate aldolase	3-8 units	
Sorbitol dehydrogenase	0-0.02 μmol/(ml h)	

Glucose-6-phosphate dehydrogenase of erythrocytes	Negative	
Creatine phosphokinase general	10-110 ME	0.60-66 mmol of inorganic phosphorus / (h·l)
CPK isozymes		
BB	Absent	
MB	4-6% of the total	
MM	94-96% of the total	

2. TASKS FOR INDEPENDENT WORK.

In the table with the test tasks, underline the keywords, select the correct answer, and justify it:

1.	A 38-year-old patient has rheumatism in the active phase. Determination of which laboratory value of blood serum has a diagnostic value in this pathology? A. Creatine B. Urea C. C-reactive protein D. Uric acid E. Transferrin	
2.	A patient who is being treated for viral hepatitis B has signs of liver failure. What blood changes indicating a violation of protein metabolism are most likely to be observed in this case? A. Absolute hyperfibrinogenemia	

	B. Absolute hypoalbuminemia C. Absolute hyperalbuminemia D. The protein composition of the blood is not changed E. Absolute hyperglobulinemia	
3.	A person performing heavy physical work in conditions of high ambient temperature has changed the amount of plasma proteins. What exactly is happening in this case? A. Dysproteinemia B. Absolute hypoproteinemia C. Paraproteinemia D. Absolute hyperproteinemia E. Relative hyperproteinemia	
4.	In a patient 12 hours after an acute attack of chest pain, a sharp increase in serum AST activity was found. Indicate the pathology for which this shift is characteristic: A. Diabetes mellitus B. Diabetes insipidus C. Myocardial infarction D. Collagenosis E. Viral hepatitis	
5.	In the study of the patient's serum, an increase in the level of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) was found. What	

	changes in the body at the cellular level can lead to this situation? A. Violation of the enzymatic systems of cells B. Damage to the genetic apparatus of cells C. Destruction of cells D. Violation of the function of energy supply of cells E. Disruption of intercellular connections	
6.	The patient complains of frequent pain in the chest and spine, rib fractures. The doctor suggested myeloma. Which of the following pathological conditions will be associated with myeloma? A. Paraproteinemia B. Hypoproteinemia C. Hyperalbuminemia D. Hypoglobulinemia E. Proteinuria	
7.	A 27-year-old patient has pathological changes in the liver and brain. A sharp decrease in blood plasma and an increase in urine copper content were detected. The diagnosis is Wilson-Konovalov disease. The activity of which enzyme in the blood serum should be investigated to confirm the diagnosis?	

	A. Alcohol dehydrogenase B. Xanthine oxidase C. Leucine aminopeptidase D. Carbonic anhydrase E. Ceruloplasmin	
8.	In hepatitis, myocardial infarction in the blood plasma of patients sharply increases the activity of alanine and aspartate aminotransferase. What are the causes of increased activity of these enzymes in the blood? A. Lack of pyridoxine B. Damage to cell membranes and release of enzymes into the blood C. Increased rate of amino acid breakdown in tissues D. Increase in the rate of synthesis of amino acids in tissues E. Increase in enzyme activity	
9.	A person suffers from diabetes mellitus, accompanied by fasting hyperglycemia of more than 7.2 mmol / l. The level of which blood protein allows to estimate the level of hyperglycemia retrospectively (for the previous 4-8 weeks before the examination)? A. Glycosylated hemoglobin B. Ceruloplasmin C. C-reactive protein	

	D. Fibrinogen E. Albumin	
10.	The patient's fasting blood glucose is 5.6 mmol / l, an hour after a sugar load - 13.8 mmol / l, and after 3 hours - 9.2 mmol / l. What pathology is characterized by such indicators? A. Hidden form of diabetes mellitus B. Thyrotoxicosis C. A healthy person D. Acromegaly E. Itzenko-Cushing's disease	
11.	A one-year-old child lags behind his peers in mental development. In the morning: vomiting, convulsions, loss of consciousness. In the blood - hypoglycemia on an empty stomach. What enzyme defect can this be due to? A. Saccharase B. Glycogen synthase C. Arginase D. Phosphorylases E. Lactase	
12.	The patient's fasting blood glucose was 5.65 mmol/l, 1 hour after a sugar load was 8.55 mmol/l, and 2 hours later was 4.95 mmol/l. Such indicators are typical for:	

	A. A healthy person B. A patient with thyrotoxicosis C. A patient with latent diabetes mellitus D. A patient with insulin-dependent diabetes mellitus E. A patient with insulin-independent diabetes mellitus	
13.	In diabetes mellitus due to activation of fatty acid oxidation processes, ketosis occurs. What disorders of acid-base balance can lead to excessive accumulation of ketone bodies in the blood? A. Metabolic acidosis B. There will be no changes C. Respiratory alkalosis D. Respiratory acidosis E. Metabolic alkalosis	
14.	A 45-year-old woman has Itzenko-Cushing's disease - steroid diabetes. At biochemical examination: hyperglycemia, hypochloremia. Which of the following processes is activated in a woman in the first place?	

	A. Glycolysis B. Glycogenolysis C. Reabsorption of glucose D. Gluconeogenesis E. Transport of glucose into the cell	
15.	During the examination, the patient was found to have an increased content of low-density lipoprotein in the blood serum. What disease can be expected in this patient? A. Atherosclerosis B. Kidney damage C. Inflammation of the lungs D. Acute pancreatitis E. Gastritis	
16.	During the examination of an adolescent suffering from xanthomatosis, familial hypercholesterolemia was found. The concentration of which lipoproteins is significantly increased in the blood in this pathology? A. HDL B. VLDL C. LDL D. Cholesterol E. Chylomicrons	
17.	A 70-year-old man suffers from atherosclerosis of the vessels of the lower	

	extremities and coronary heart disease. The examination revealed a violation of the lipid composition of the blood. Excess of which lipoproteins in the blood plasma is the main link in the pathogenesis of atherosclerosis? A. Chylomicrons B. Low density lipoprotein C. High density D. Cholesterol E. Intermediate density	
18.	A 49-year-old patient, a driver by profession, complains of unbearable compressive pain behind the sternum, which "gives" to the neck. The pain started 2 hours ago. Objectively: severe condition, pallor, weakened heart sounds. Laboratory tests showed high activity of creatine kinase and LDH1. What disease is characterized by such symptoms? A. Angina pectoris B. Acute pancreatitis C. Gallstone disease D. Diabetes mellitus E. Acute myocardial infarction	
19.	A healthy person's blood plasma contains several dozen proteins. In case of diseases of the body, new proteins appear, in	

	particular, "acute phase proteins". These proteins are: A. Immunoglobulin G B. Immunoglobulin A C. Fibrinogen D. Prothrombin E. C-reactive protein	
20.	Biochemical analysis of the blood of a patient with hepatolenticular degeneration (Wilson-Conovalov disease) revealed a decrease in ceruloplasmin. This patient will have an increased concentration of ions in the serum: A. Potassium B. Calcium C. Phosphorus D. Sodium E. Copper	
21.	A 49-year-old patient with acute pancreatitis has a threat of pancreatic necrosis, which was accompanied by the entry of active pancreatic proteinases into the blood and tissues and the breakdown of tissue proteins. What protective factors of the body can inhibit these processes? A. Ceruloplasmin, transferrin B. Hemoplexin, haptoglobin C. a2-macroglobulin, a1-antitrypsin D. Cryoglobulin, interferon	

	E. Immunoglobulin	
22.	Electrophoretic examination of the blood serum of a patient with pneumonia showed an increase in one of the protein fractions of the blood. Specify it: A. Alpha1-globulins B. Albumin C. Beta-globulins D. Gamma globulins E. Alpha2-globulins	
23.	In a laboratory study of the blood of a 44-year-old patient, it was found that the plasma protein content is 40 g / l. How will this affect transcapillary water metabolism? A. Reduced filtration, increased reabsorption B. The exchange does not change C. Filtration and reabsorption decrease D. Filtration increases, reabsorption decreases E. Filtration and reabsorption increase	

3. <u>LITERATURE. See page 320.</u>

LESSON №14

14. TOPIC: BIOCHEMISTRY OF NERVOUS TISSUE AND IMMUNE SYSTEMS

2. INFORMATION MATERIAL.

The nervous system is an exceptionally complex and unique biological structure that controls important body functions and provides a regulatory and integrative role in relation to the processes occurring in the human body.

Nervous tissue consists of three main types of cells: nerve cells (neurons or neurocytes), neuroglia (macroglia) that fills all the spaces between them, and mesenchymal elements (microglia, which includes glial macrophages - Ortega cells). The bulk of the brain is represented by the first two types of cellular elements.

Neurons are the structural and functional unit of the nervous system. They are highly specialized cells that do not divide during life. They perceive, process, encode, store, and transmit information, establishing numerous connections between themselves and with cells in other organs. The unique features of neurons are their ability to perceive stimuli, enter a state of excitation, generate and conduct (spread) electrochemical nerve impulses and transmit them at special places of intercellular contacts (synapses) with the help of neurotransmitters (intermediary substances synthesized by neurons themselves).

The number of neurons in the human brain is about one hundred billion (1011). One neuron can have up to 10,000 synapses. Neurons are concentrated in the gray matter, which occupies 60-65% of the entire brain, while the white matter of the central nervous system and peripheral nerves consists mainly of elements of neuroglia and its derivative, myelin.

The number of neuronal processes varies, but they are divided into two types according to their structure and function. One type, short, highly branched processes, is called dendrites (Greek: δένδρον - tree, branch). A nerve cell can have from one to several tens or even hundreds of dendrites. Their main function is to collect information from many other neurons. It is interesting that a child is born with a

limited number of dendrites (inter-neuronal connections), and the increase in brain weight that occurs during the stages of its postnatal development is realized by increasing the mass of dendrites and glial elements.

Another type of nerve cell processes are axons (Greek: ἀξον - axis). There is only one axon in a neuron and it is a more or less long process that branches only at the distal end, forming axonal terminals (endings). The place in the neuron where the axon starts is of particular functional importance and is called the axonal tubercle. It is here that the action potential is generated - a specific electrical response of an excited nerve cell.

The system of inter-neuronal and peripheral connections is carried out through specific formations - **synapses,** which provide signal transmission and modulation from the presynaptic to the postsynaptic membrane through chemical and electrical processes.

A high **level of energy metabolism in** nervous tissue is a characteristic feature of metabolic processes. In terms of oxygen and glucose consumption, the brain ranks first among human organs. It is important to note that glucose is the predominant substrate of oxidation in nervous tissue and cannot be replaced by other substrates of energy metabolism. The brain's own carbohydrate reserves are very small, which explains the high sensitivity of nervous tissue to hypoglycemia and hypoxia. The high intensity of energy metabolism is the main factor that ensures the course of such specific processes as the transmission of nerve impulses, storage and processing of information, and integrative brain activity.

Neurospecific proteins

Neurospecific proteins are special structural components of nervous tissue that are characteristic of it and distinguish this tissue from others. They are directly or indirectly involved in various functions of the nervous system, such as generation and conduction of nerve impulses, processing and storage of information, synaptic transmission, cellular cognition, adhesion, reception, etc.

The S-100 protein, so named because of its ability to remain in a dissolved state even in a saturated solution of ammonium sulfate (from the English word "*soluble 100%")*, is not a single protein, but a whole family of proteins, the polypeptide chains of which are represented by at least 20 tissue-specific monomers that differ from each other in mass, charge and number of calcium-binding centers (from 2 to 8). Proteins are involved in the regulation of most major membrane, cytoplasmic and nuclear metabolic processes. Their regulatory potential is realized through secondary messenger systems, primarily through changes in the concentration of intracellular ions Ca^{2+}.

Glial fibrillary acidic protein (GFAP) is an exclusively glial protein that is specific to the CNS, as it is not found in the peripheral NS. Moreover, its content in the white matter of the brain is higher than in the gray matter.

The most well-known neurospecific cell adhesion molecules are N-CAM (***neural cell adhesion molecule)***, NG-CAM (***neural glial cell adhesion molecule)***, MAG (***myelin-associated glycoprotein),*** N-cadherin, and AMOG (adhesive molecule of glia).

Lipids of nervous tissue

The nervous tissue is dominated by polar phospholipids with a small amount of cholesterol and its esters.

Many lipids in nervous tissue are closely related to ***proteins***, forming complex systems such as ***proteolipids***. They are not only structural components of the nervous tissue, but also one of the most important factors of its functional activity.

Sphingomyelins, cerebrosides, gangliosides, and triphosphoinositides are specific lipids of nervous tissue.

The lipid composition of nervous tissue membranes is genetically determined. The location of lipid molecules in different layers of the membrane occurs in accordance with their stereoconfiguration, total charge, composition, degree of hydration of polar groups, etc., which creates structural and functional asymmetry of the membranes.

Amino acid pool of nervous tissue

Free amino acids found in brain tissue play several important functions:

- is a source of protein synthesis, as well as some protein and peptide hormones, vitamin derivatives (NADH), nucleotides, biologically active amines (catecholamines, serotonin, histamine, GABA)
- how neurotransmitters are directly involved in the implementation of inter-neuronal synaptic connections (glutamate, glycine, aspartic acid, taurine, etc.)
- Utilization of ammonia released during nerve cell excitation
- energy role, since some of them (aspartate, glutamate, alanine, etc.) can be converted into intermediates of the tricarboxylic acid cycle

The total content of free amino acids in brain tissue is significantly higher than their concentration in blood plasma and cerebrospinal fluid - 34 μmol/g (on average).

Glutamate is found in the brain in very large quantities (more than 10 μmol/g tissue) and performs a variety of functions:

- is one of the main excitatory mediators in the cortex, hippocampus, striatum and hypothalamus
- participates in the regulation of memory processes
- a glutamate derivative, cyclic pyroglutamate, is included in a number of ***neuropeptides, such as*** luliberin, tyroliberin, neurotensin, bombesin, etc.
- transamination and oxidative deamination reactions of glutamate play an energetic role (they are suppliers of ***α-ketoglutarate, a*** component of the tricarboxylic acid cycle).

Glutamic acid, aspartic acid, and cysteine are potential excitatory neurotransmitters, but their decarboxylation products are not: ***GABA, beta-alanine, taurine, and the amino acid glycine act as inhibitory mediators.***

The amino acids ***phenylalanine*** and ***tyrosine*** are used in nervous tissue to a greater extent for the formation of neurotransmitters: ***dihydroxyphenylalanine (DOPA), dopamine, norepinephrine,*** and ***epinephrine. Tryptophan*** in brain neurons is a precursor of the neurotransmitters ***tryptamine*** and ***serotonin,*** but in the

pineal gland, tryptophan is considered the main substrate for the synthesis of the ***hormone melatonin,*** which controls the biological rhythms of the human body and the secretion of pituitary hormones.

Sulfur-containing amino acids, primarily ***methionine, are*** used in brain neurons to produce the amino acid ***cysteine,*** which is a participant in the synthesis of short peptides that function as coenzymes (glutathione, CoA), hormones (vasopressin, oxytocin, neurophysin, bombesin, etc.), and taurine.

Features of carbohydrate metabolism in nervous tissue

In the mitochondria of brain cells, the only source of acetyl-CoA for the ***tricarboxylic*** acid cycle is the ***oxidative decarboxylation of*** pyruvic ***acid*** with the participation of enzymes of the pyruvate dehydrogenase complex. Nervous tissue is very sensitive to any disruption of the functioning of the components of this complex.

The human brain needs about 100 g of glucose per day.

The first reaction of the involvement of free glucose, which enters the brain cells from the blood, in various metabolic processes is its phosphorylation reaction, which is catalyzed by ***hexokinase,*** resulting in the formation of glucose-6-phosphate. Thus, unlike all other tissues, the hexokinase reaction is of particular importance in the nervous tissue for the regulation of carbohydrate metabolism and, consequently, for energy production.

However, the key enzymes of glucose metabolism in nervous tissue are ***phosphofructokinase*** and ***isocitrate dehydrogenase***.

Thus, the specificity of energy catabolism of nervous tissue lies mainly in the peculiarities of the mechanisms of regulation and in the characteristic ratios of the activity of key enzymes located at the intersection of different metabolic pathways.

During oxygen starvation, the brain receives energy only through anaerobic glycolysis, so the cessation of oxygen access even for 10-15 seconds disrupts the energy of nerve cells, which in the whole body is expressed by the onset of unconsciousness.

Metabolism of amino acids and proteins in different parts of the nervous system

Brain proteins are in a state of active renewal, as evidenced by the rapid incorporation of radiolabeled amino acids into their molecules. However, the rate of synthesis and decay of protein molecules is different in different parts of the brain. The proteins of the gray matter of the cerebral hemispheres and the proteins of the cerebellum are characterized by a particularly high rate of renewal. In areas of the brain rich in conductive structures (white matter), the rate of synthesis and breakdown of protein molecules is lower.

Different functional states of the central nervous system result in changes in the intensity of protein renewal. The active state of neurons is always accompanied by an increase in the amount of proteins and RNA, while in inhibitory states and neuronal fatigue, the content of these substances decreases. In the process of recovery, everything returns to the initial level or even exceeds it. A higher intensity of protein renewal is characteristic of phylogenetically younger and more functionally active brain structures.

Against the background of the generally high renewability of brain proteins, a few rather inert proteins deserve special attention. These include **histones of** neocortical neurons, cationic chromatin proteins.

Glutamic acid rightfully occupies a central place in the metabolism of amino acids in the brain (it is used in transamination reactions and is closely related to intermediate metabolites of the tricarboxylic acid cycle, participates in the temporary neutralization of ammonia, in the synthesis of glutathione, one of the components of the body's antioxidant system and the inhibitory neurotransmitter GABA).

The sulfur-containing amino acids ***methionine*** and ***cysteine are of*** great importance for the normal functioning of the brain. For example, ***S-adenosylmethionine*** (the active form of methionine) is a source of labile methyl groups necessary for the synthesis of acetylcholine, lecithin, methylation of catecholamines, histamine, and nucleic acids.

Lipid metabolism

Nerve tissue lipids are also constantly renewed. The synthesis of cerebrosides and gangliosides proceeds at a high rate during the period of fiber myelination in the developing brain. In adults, almost all cerebrosides (up to 90%) are found in myelin sheaths, and gangliosides are found in neurons.

Sphingolipids, especially gangliosides and cerebrosides, play an extremely important role in the processes of communication between the nerve cell and its environment.

In the nervous tissue, ***galactoceramides*** predominate among cerebrosides and their sulfoesters (sulfatides), especially in the white matter, axonal membranes, and myelin. Galactoceramides and galactosulfatides are most actively synthesized during fiber myelination, and gangliosides - during neuronal differentiation. Gangliosides are mainly found in gray matter, in cells. ***Biological role and importance of sphingolipids in nervous tissue***:

1. they are receptors for external signals, including some dangerous bacterial toxins
2. together with glycoproteins are responsible for cell surface specificity, cell recognition and adhesion
3. are important for establishing "correct" intercellular connections in the formation of nervous tissue
4. are involved in the functioning of mature nervous tissue, in particular in synaptic signal transmission, in reactions of adaptation and adaptation
5. some of the gangliosides exhibit moderate hapten properties and therefore may be involved in certain allergic and immunological processes

Some lipids have a protective function. For example, gangliosides are also active **antioxidants** - inhibitors of peroxidation. When brain tissue is damaged, they contribute to its repair.

The importance of aerobic glucose oxidation in the energy supply of GM

No other organ absorbs blood glucose at such a high rate and in such an amount as the brain, and no other tissue in the body has such an urgent need for this oxidation substrate to maintain a normal functional state. The brain uses up to 70% of the glucose that is synthesized in the liver and ingested with food. Calculations show that about 85-90% of the glucose used by the adult brain is completely oxidized to CO_2 and H_2O. About 5% is consumed in glycolysis reactions with the formation of lactic acid and only 5-7% in other reactions (synthesis of glycogen, ceramide part of glycolipids and glycoproteins, neurotransmitters). Glucose reserves in the brain are very small compared to the high rate of oxidation, which requires a constant supply of glucose from the blood.

The first step on the way to the inclusion of free glucose, which enters the brain from the blood, in various metabolic transformations is the **phosphorylation reaction**. It is catalyzed by ***hexokinase*** - GK (ATP: D-glucose-6-phosphotransferase). For the regulation of energy metabolism in the brain, the hexokinase reaction is of particular importance because it is the main supplier of glucose-6-phosphate (90-95%). The bulk of glucose-6-phosphate is used in aerobic glycolysis reactions. An important step in controlling the rate of glycolysis is the ***phosphofructokinase reaction***. The final stages of glycolysis in the brain, which occur via fructose-1,6-diphosphate formation reactions, are catalyzed by enzymes whose activity is sufficiently high. Therefore, the subsequent stages of the phosphotriose conversion do not limit the overall rate of aerobic glycolysis in brain tissue. The final product of aerobic glucose oxidation is pyruvic acid (pyruvate).

The high rate of glucose and oxygen utilization by the brain is combined with the intensive formation of macroergic compounds. Among the energy-rich substances in the brain, the main share belongs to the components of the adenine nucleotide system and creatine phosphate. The main component of the adenine nucleotide pool in the nervous tissue is ATP.

Chemical bases of pulse generation and conduction

The phenomena of cellular electrical polarization are caused by the uneven distribution of K^+ and Na^+ ions on both sides of the cell membrane. The membrane has a selective permeability: higher for K^+ ions and much lower for Na^+ ions. In addition, there is a mechanism in nerve cells that maintains the intracellular content of sodium ions at a low level despite the concentration gradient. This mechanism is called the sodium pump.

At rest, the inner side of the cell membrane is electronegatively charged in relation to the outer surface.

During excitation caused by a particular agent, the permeability of the nerve cell membrane (axon) selectively changes: it increases for Na^+ ions (approximately 500 times) and remains unchanged for K^+ ions. This leads to a negative charge on the outer surface of the cell membrane, and the inner surface of the membrane acquires a positive charge; the cell membrane (in particular, the axon membrane, i.e., the nerve fiber) is recharged, and an ***action potential*** arises. After the impulse is delivered, the cell returns to its resting state. During this period, the Na^+ ions that entered the neuron during excitation are replaced by K^+ ions.

Another equally important process for nervous tissue is the transmission of a nerve impulse from one nerve cell to another or the effect on effector cells, which occurs through synapses.

A synapse is a functional contact of specialized areas of the plasma membranes of two excitable cells. A synapse consists of a presynaptic end, which contains a large number of vesicles with neurotransmitters, a presynaptic membrane, a synaptic cleft 10-50 nm wide, and a postinaptic membrane with receptor proteins. The cell membranes at the point of contact are thickened in the form of plaques. The nerve impulse, moving along the axon, reaches the presynaptic membrane, but it is unable to overcome the obstacle that has arisen before it - the synaptic cleft. Therefore, here the electrical signal is converted into a chemical signal.

The presynaptic membrane contains special channel proteins that respond to the membrane potential by changing their conformation and forming calcium

channels. As a result, Ca^{2+} ions pass through the presynaptic membrane into the nerve ending, which leads to the fusion of 200-300 vesicles filled with the appropriate chemical mediator (neurotransmitter) with the plasma membrane. Then, by exocytosis, the neurotransmitter is secreted into the synaptic cleft and interacts with receptor proteins located on the surface of the postsynaptic membrane.

The excitatory postsynaptic potential is triggered:

1. ***Opening of sodium channels,*** which allows a large amount of sodium cations to enter the postsynaptic cell.

2. ***Reduced conductance through chloride*** or ***potassium channels*** reduces the diffusion of negatively charged Cl^- ions into the postsynaptic neuron and the diffusion of positively charged K^+ ions outward, and maintains a more positive than normal membrane potential, which promotes excitation.

3. Various ***changes in the intracellular metabolism of the*** postsynaptic neuron, leading to a disturbance in cellular activity and, in some cases, an increase in the number of excitatory or decrease in the number of inhibitory membrane receptors.

The inhibitory postsynaptic potential is triggered:

1. ***Opening of channels for chlorine ions***, which allows these anions to diffuse rapidly from the outside into the postsynaptic neuron, thus increasing the amount of negative charge inside it.

2. ***Increasing the conductivity of the membrane for potassium ions*** allows positive ions to diffuse outward, which leads to an increase in the amount of negative charge inside it.

3. Activation of certain enzymes that are responsible for cellular metabolic functions and increase the number of inhibitory receptors or decrease the number of excitatory synaptic receptors.

Neurotransmitters

A neurotransmitter is a substance that is synthesized in a neuron and contained in presynaptic endings, released into the synaptic cleft in response to a nerve impulse and acts on specialized receptor sites in the postsynaptic cell, causing a change in the membrane potential and/or metabolism of the cell.

The neurotransmitter must meet the following **criteria**:

- the substance must be released from the neuron when it is excited;
- The neuron must have enzymes to synthesize this substance;
- postsynaptic cells have receptors for this substance;
- an exogenous analog mimics the action of a neurotransmitter.

According to their chemical structure, neurotransmitters **are divided into:**

- Amines: monoamines (acetylcholine, serotonin, histamine) and catecholamines (epinephrine, norepinephrine, dopamine).
- Amino acids: GABA, glycine, glutamic acid, aspartic acid.
- Neuropeptides: enkephalins, endorphins, substance P.

Acetylcholine is a biologically active substance widely distributed in nature. In organs and tissues, it causes effects characteristic of the excitation of the parasympathetic elements of the ANS (lowering blood pressure, slowing the heart rate, increasing gastric and intestinal motility, constriction of the pupils, etc.)

Serotonin is a breakdown product of the amino acid tryptophan, found in all tissues, mainly in the digestive tract and central nervous system (CNS), as well as in platelets. It affects vascular tone, which is associated with peripheral vasoconstriction, increases platelet aggregation, reducing bleeding time. Participates in regulation of digestive, excretory, endocrine systems (regulates gastrointestinal motility, mucus secretion, causes spasm of damaged vessels, etc.)

Histamine is an organic compound, a biogenic amine. It is found in large quantities in an inactive, bound form in various human organs and tissues (lungs, liver, skin), as well as in platelets and leukocytes. It is formed in the body from histidine and is an essential amino acid for the child's body, as it is not synthesized

in the body. In case of histidine deficiency, hemoglobin formation in the bone marrow decreases. Histamine is released during anaphylactic shock, inflammatory and allergic reactions. It causes dilation of capillaries and increase in their permeability, narrowing of large vessels, contraction of smooth muscles, and sharply increases hydrochloric acid secretion in the stomach. Its release in allergic reactions leads to skin redness, itching, blistering, etc.

Adrenaline is a hormone of the adrenal medulla, which, when released into the bloodstream, increases oxygen consumption by organs and tissues, participates in the mobilization of glycogen, the breakdown of which leads to an increase in blood sugar levels, stimulates metabolism (protein, carbohydrate, fat, mineral), increases blood pressure (mainly due to narrowing of small peripheral vessels), accelerates and strengthens heartbeat, accelerates respiratory rhythm, slows intestinal motility, etc. д. During emotional experiences, intense muscle work, cooling, lowering of blood sugar, its content in the blood rises sharply. In some diseases of the internal organs, nervous system, and endocrine glands, the level of adrenaline in the body increases or decreases, which complicates the course of the disease.

Norepinephrine is a precursor to adrenaline. By the nature and strength of its action on the heart, blood vessels, smooth muscles, and carbohydrate metabolism, it has hormone properties and is close to adrenaline. In medical practice, it is used to reduce blood pressure, collapse, shock, blood loss, etc.

Dopamine is also a precursor to norepinephrine. Under its influence, peripheral vascular resistance increases (not as much as under the influence of norepinephrine) and systolic blood pressure increases, heart rate increases, and cardiac output increases.

Gamma-aminobutyric acid (GABA) is the most common inhibitory neurotransmitter in the central nervous system, which is able to modify the properties of the postsynaptic membrane in such a way that the ability of the cell to generate excitation is partially or completely suppressed. It improves the dynamics of nervous processes in the brain, increases the productivity of thinking, improves

memory, and has a moderate psychostimulant, antihypoxic, and anticonvulsant effect. It helps restoring speech and motor functions after cerebral circulation disorders. It has a moderate hypotensive effect and reduces the severity of symptoms caused by hypertension (dizziness, insomnia). In patients with diabetes mellitus, it reduces blood glucose level, and in case of normal blood sugar level it often causes its increase.

Glycine is a component of many proteins and biologically active compounds, is an inhibitory neurotransmitter and a regulator of metabolic processes in the brain. It normalizes the state of the nervous system during periods of hyper-excitement, overwork and intoxication, has anti-stress effect, improves mental and physical performance, increases muscle tone, promotes concentration and restores memory.

Glutamic acid is present in the body as part of proteins, a number of low-molecular-weight substances and in free form. It plays an important role in nitrogen metabolism (binds and removes ammonia, which is toxic to the body). Regulates metabolism and stimulates redox processes in the brain, changing the functional state of the nervous and endocrine systems.

Aspartic acid is an excitatory neurotransmitter in the neurons of the cerebral cortex.

Opioid peptides

It is known that the feeling of pleasure, joy, and happiness is provided by three classes of substances if they appear in certain parts of the brain in sufficient concentration:

1. The neurotransmitters discussed above are **serotonin, dopamine, norepinephrine,** and others.

2. **Enkephalins** and **endorphins** are short oligopeptides formed by cleaving fragments from much larger precursor proteins.

3. **Arachidonic acid derivatives** (anandamide and 2-arachidonoyl glycerol).

Endorphins - they are called "the body's own drugs" or "pleasure hormones". To date, 18 types of opiate-like substances have been identified in the human brain.

They perform many different functions in the body, the most important of which is the regulation of pain. They affect emotional reactions, causing a feeling of pleasure, regulate hunger, participate in memory processes, in the body's response to stress factors, and to alcohol. The lack of endorphins is observed in all chronic diseases, the effects of stress, depression, and chronic fatigue syndrome.

Enkephalins are peptide substances with morphine-like effects on the body. They can inhibit the interneuronal transmission of pain impulses, reducing the motor activity of the gastrointestinal tract, the speed of the central nervous system and contribute to pain relief.

Opioid receptors are a type of membrane receptors in nervous tissue that are bound to G**i** protein. When they are activated, adenylate cyclase is inhibited, which leads to a decrease in cAMP synthesis, presynaptic potential-dependent calcium channels are closed, which helps to reduce the release of excitatory neurotransmitters into the synapse, and activation of potassium channels of the postsynaptic membrane causes its hyperpolarization. All of this ultimately leads to a single total end result - a significant decrease in the sensitivity of the postsynaptic neuron to the action of excitatory mediators.

There are three main groups of opioid receptors:

- *mu*(μ1 and **μ2 *)-receptors*** localized in the nuclei of the brain stem, hypothalamus, thalamus, somato-sensory cortical areas, and spinal cord (their ligands are endorphins);

- *delta*(δ)-*receptors of* limbic structures, septum and hypothalamus (ligands - enkephalins);.

- *kappa*(κ1 and **κ2 *)-receptors of*** the spinal cord, hypothalamus, and cortex (dynorphins are the ligands).

Some recent studies have reported the isolation of ***sigma*(σ)**- and ***ipsilon*(υ)-*receptors***.

Psychotropic medications

The pathochemical conditions of mental disorders are numerous, diverse and extremely complex in terms of their mechanisms of occurrence and development. Certain mental illnesses and psychoemotional disorders are largely determined by disorders in the functioning of certain mediator-receptor systems of the human brain. The pathogenesis of schizophrenia and schizoactive psychosis is associated with hyperfunction of dopaminergic nuclei. States of psychoemotional stress, anxiety, and fear are associated with stimulation of adrenergic structures. Disorders of sleep cycles are associated with dysfunction of the serotonergic system, pain syndrome - with the state of the antinociceptive system of opiate receptors and opioid neuropeptides.

Psychotropic medications are pharmaceuticals used in case of mental disorders.

The analysis of the general molecular and cellular mechanisms of physiologically active compounds, including drugs, as well as the structure and molecular organization of mediator and receptor structures of interneuronal synapses allows us to identify the following **links in synaptic transmission in the** brain:

- Enzymatic synthesis and breakdown of neurotransmitter;
- Deposition of neurotransmitter in vesicles of neurosynaptic endings;
- Release of neurotransmitter into the synaptic cleft;
- Interaction of the neurotransmitter with postsynaptic ionotropic and/or metabotropic receptors, and the inclusion of the corresponding sequence of biochemical and biophysical reactions in the membrane, cytoplasm and organelles of the sensitive neuron;
- Interaction of neurotransmitter with presynaptic membrane structures responsible for its reuptake and enzymatic degradation.

The most common groups of psychotropic drugs are neuroleptics, antidepressants, anxiolytics (tranquilizers), and nootropics.

Neuroleptics (antipsychotic drugs) are medicines used to treat psychoses, mainly schizophrenia, as well as other exogenous and endogenous mental disorders manifested by severe psychoemotional disorders with delusions, hallucinations, and agitation. The neurochemical mechanisms of the therapeutic effects of neuroleptics are based on their antagonistic effect on dopamine receptors, which are localized mainly in the limbic system of the brain.

Antidepressants (thymoleptics) are psychopharmacological agents used to treat depression of various genesis. The neurochemical basis of the effect of antidepressants of different structures on the central nervous system is their ability to stimulate monoaminergic transmission in the brain, which is achieved by increasing the synaptic concentration of norepinephrine and/or serotonin.

Anxiolytics (tranquilizers) are drugs that have a calming effect and relieve mental and emotional stress and anxiety.

The neurochemical mechanisms of the central pharmacological effects of anxiolytics are associated with their interaction with GABA receptors of postsynaptic membranes of GABAergic neurons in the brain, which potentiates the inhibitory effects of gamma-aminobutyric acid. The interaction of benzodiazepines (the most common anxiolytics) with the BD-binding receptor sites of the "GABA-receptor-chloride channel" allosterically activates the actual GABA-receptors, which, in turn, leads to the opening of chloride channels and hyperpolarization of the postsynaptic membrane, i.e., realizes the inhibitory effects of benzodiazepines.

Nootropics are drugs that specifically affect the higher integrative functions of the brain, improve memory, facilitate learning, stimulate intellectual activity, increase resistance to damaging factors, and optimize cortical-subcortical connections. The main neurochemical mechanisms of action of nootropic drugs are considered to be the influence on metabolic and bioenergetic processes in nerve cells, their interaction with neurotransmitter systems of the brain. There is a group of "true" nootropic drugs, for which the ability to improve mnemonic functions is the main, and sometimes the only effect, and a group of mixed-action nootropic drugs, in which the mnemonic effect is complemented and often overlapped by

other, no less significant manifestations of action. A number of nootropic drugs have a fairly broad spectrum of pharmacological activity: antihypoxic, antioxidant, membrane stabilizing, anxiolytic, sedative, anticonvulsant, antiasthenic, adaptogenic, psychostimulant, and antiplatelet.

Nootropics affect the synthesis of phospholipids, inhibit the formation of free radicals, lipid peroxidation, and increase resistance to hypoxia and toxic substances. The result of the complex action of nootropic drugs is an increase in bioelectrical activity and integrative brain activity, which is manifested by characteristic changes in cortico-subcortical control, improvement of information exchange in the brain, positive effect on the formation and reproduction of memory, perception of attention, thinking, increased learning ability, and activation of intellectual activity. In addition, nootropics have a positive effect on the autonomic nervous system in parkinsonism, epilepsy and other diseases.

Nootropic drugs can improve cognitive functions both in healthy people and especially in various diseases. They do not cause psychomotor excitement, depletion of the body's functional capabilities, addiction, or addiction.

2. TASKS FOR INDEPENDENT WORK.

In the table with the test tasks, underline the keywords, select the correct answer, and justify it:

1.	The main structural and functional unit of the nervous system is the neuron: A. Neuron B. Astrocyte C. Dendrite D. Axon	

	E. Neuroglia	
2.	Inter-neuronal and peripheral connections are made through specific formations: A. Synapses B. Receptors C. Lymph nodes D. Blood-brain barrier E. Nucleotides	
3.	What amino acid plays the role of a neurotransmitter in nervous tissue? A. Glutamate B. Arginine C. Alanine D. Tryptophan E. Cysteine	
4.	The inhibitory neurotransmitter in the CNS is: A. GABA, glycine B. Glutamate, aspartate C. Glutamine, asparagine D. Valine, leucine E. Cysteine, methionine	
5.		

	The main source of the neurotransmitter glutamate pool is: A. Glutamine B. Alanine C. Cysteine D. GABA E. Glycine	
6.	The main energy source for the brain is: A. Glucose B. Fructose C. Galactose D. Glycogen E. Maltose	
7.	The depressive state is associated with systemic depression: A. Serotonergic system B. Dopaminergic C. GABAergic D. Histamine E. Adrenaline	
8.		

	The energy needs of the brain are met mainly by oxidation: A. Proteins B. Glucose C. Triglycerides D. Glycolipids E. Higher fatty acids	
9.	Indicate the main pathway of glucose utilization in the brain: A. Pentose phosphate pathway B. Lipolysis C. Anaerobic glycolysis D. Aerobic glycolysis E. Glycogenesis	
10.	The interaction of GABA with ionotropic GABA receptors leads to the opening of fast ion channels and entry into the postsynaptic neuron: A. Potassium ions	

	B. Calcium ions C. Sodium ions D. Chlorine ions E. Magnesium ions	
11.	The increase in brain mass that occurs during the stages of its postnatal development is realized mainly by: A. Increase in the body weight of neurons B. Increase in the mass of dendrites and glial elements C. Increase in the amount of cerebrospinal fluid D. Increase in the mass of dendrites and neuronal axons E. Accumulation of glycogen and other nutrients in brain cells	
12.	The "fusion" of vesicles filled with the corresponding neurotransmitter in the presynaptic nerve ending with its membrane during depolarization and exocytosis of the neurotransmitter into the synaptic cleft leads to the "fusion" of the vesicles:	

	A. Increase in the concentration of Ca^{2+} in the nerve ending B. Decrease in the concentration of Ca^{2+} in the nerve ending C. Increase in the concentration of Na^{+} in the nerve ending D. Increase in the concentration of K^{+} in the nerve ending E. Зменшення концентрації Na^{+} in the nerve ending	
13.	Glutamate and aspartate open sodium channels through ionotropic receptors, which leads to rapid entry of Na^+ ions into the postsynaptic neuron and depolarization of the postsynaptic membrane. Name another mediator that acts in a similar way: A. Dopamine B. Serotonin C. Glycine D. Acetylcholine E. Norepinephrine	
14.	Enkephalins are structured as follows:	

	A. Glycoproteins B. Pentapeptides C. Phospholipids D. Cerebrosides E. Octapeptides	
15.	Select the enzyme involved in the synthesis of serotonin A. 5-oxytryptophan decarboxylase B. Dopamine beta-hydroxylase C. Choline acetyltransferase D. Tyrosine hydroxylase E. Glutamate decarboxylase	
16.	Choose an opioid peptide that has a pronounced analgesic activity: A. Dopamine B. Glutathione C. Serotonin D. Endorphin E. Acetylcholine	

3. <u>LITERATURE: See page 320.</u>

LESSON №15

15. TOPIC: THE ROLE OF THE KIDNEYS IN THE REGULATION OF WATER-SALT METABOLISM. NORMAL AND PATHOLOGICAL COMPONENTS OF URINE

2. <u>INFORMATION MATERIAL.</u>

The kidneys are paired bean-shaped organs located on both sides of the spine in the lumbar abdomen. The weight of each kidney in an adult is about 150 g. Kidney tissue contains a lot of water (about 84%), which indicates a high level of metabolic processes. The high intensity of oxidative processes in the kidneys is evidenced by their ability to absorb a significant amount of oxygen (up to 10% of the total oxygen required by the body). The main energy source for the kidneys is carbohydrates, although there is very little glycogen in the kidney tissue. Glycolysis, ketolysis, aerobic oxidation, and phosphorylation are intensively carried out in the kidneys, which leads to the most efficient use of energy and the formation of the largest amount of ATP. Aerobic metabolism dominates in the renal cortex, and anaerobic metabolism dominates in the cerebral cortex.

The kidneys perform **basic functions**:

1. Excretory;
2. Regulate water and salt balance;
3. Regulate the acid-base balance;
4. Regulate the osmotic pressure of body fluids;
5. Regulate the body's blood pressure;
6. Stimulate erythropoiesis.

Water and mineral metabolism includes the processes of intake, absorption, distribution and excretion of water and salts from the body. Water-mineral metabolism ensures the constancy of ionic composition, acid-base balance, volume of body fluids, osmotic pressure, i.e. the main parameters of homeostasis.

A constant dynamic equilibrium between the amount of water entering and leaving the body is a prerequisite for life. This is the **body's water balance**. If less

water is excreted than entered the body, this is a positive balance: it is observed in case of edema, with a significant weakening of cardiac activity, starvation If more water is excreted, this is a negative balance. This is observed in case of renal dysfunction, pituitary diseases.

The largest amount of water is excreted *by the kidneys* (about 1200-1500 ml per day with urine), when 200-500 ml is excreted with sweat, 300-500 ml through the lungs, and 250-300 ml with feces.

In order to understand the role of the kidneys in water and salt metabolism, it is necessary to understand the mechanism of urine formation.

Formation of urine

The kidneys receive a large amount of blood, from which urine is formed through complex processes of filtration and reabsorption.

Filtration takes place in the capsules. The inflow artery is larger in diameter than the outflow artery, and therefore the blood pressure in the capillaries of the glomerulus is quite high (70-80 mm Hg). Due to this high pressure, blood plasma, along with inorganic and organic substances dissolved in it, passes through the thin capillary wall into the capsule cavity. Substances with relatively small molecular diameters are filtered out. Large molecules (proteins, fats) and blood cells remain in the blood. Thus, as a result of filtration, a liquid called **primary urine is** formed in the renal capsule cavity, which includes all components of blood plasma (salts, amino acids, glucose, and other substances), except for proteins, as well as urea and uric acid.

A day produces 150-180 liters of primary urine.

From the capsules, primary urine enters the tubules. As it passes through the tubules, the epithelial cells of their walls **absorb** a significant amount of water and substances needed by the body into the bloodstream. In contrast to filtration, it occurs due to the active activity of the tubular epithelial cells with energy expenditure and oxygen absorption. Some substances (glucose, amino acids) are completely reabsorbed, other substances (mineral salts) are absorbed from the

tubules into the blood in the amounts necessary for the body, and the rest is excreted. After reabsorption, the so-called **secondary urine is** formed, which contains more than 200 substances (nitrogenous and nitrogen-free), including urea, uric acid, creatinine, enzymes, vitamins, hormones, pigments (urochrome, urochromogen, uroerythrin, urobilinogen); amino acids (glutamic, aspartic acids, glutamine, histidine); conjugates (hypuric, phenaceturic, indica) salts of ammonium, sodium, potassium, calcium, magnesium; inorganic (hydrochloric, phosphatic, sulfate) and organic (oxalic, glucuronic, succinic) acids; salts of organic acids (oxalates, urates); trace elements (iodine, cobalt, zinc, ferric, copper), phenols and their esters; neutral sulfur, etc. Normal kidney function does not contain protein and glucose in secondary urine; their appearance indicates a kidney disorder. A small amount of secondary urine is produced - about 1.5 liters per day.

Thus, **urine production is a** continuous process in which the kidneys perform work that requires a significant amount of energy.

The biological role of water

1. A universal solvent, it dissolves most organic and inorganic substances due to the fact that water molecules are dipolar.

2. Water plays an important role in maintaining the unique structure and function of cellular organelles due to its ability to form hydrogen bonds, change electrostatic and hydrophobic bonds.

3. Water is an essential component of biochemical processes related to hydrolysis and hydration.

4. Water maintains the constancy of the composition of the internal environment of the body - homeostasis.

5. It is an important factor in thermoregulation. The content of water in the body as a heat-consuming substance contributes to the constancy of the thermal regime of the human body.

The human body's water requirement is 2.5-3 liters, depending on age, gender, and ambient temperature. A child's body consumes more water because it has a more

intense metabolism and higher hydrophilicity of proteins. An adult needs 30-50 g of water per 1 kg of body weight, a child 100-150 g.

The human body can survive without food for up to two months, without water for 12-15 days, and the loss of 20-25% of water leads to death.

The bulk of water is absorbed in the intestines, mainly in the colon, and transported to tissues and organs (liver, muscles, skin), resulting in a constant water content.

Distribution of water in the body. 72% of H_2O is in the cells and is called cellular, 28-30% is in the intercellular space, 8-10% is in the free state in biological fluids: blood plasma, cerebrospinal fluid, and joint fluids. It is labile and has solvent properties.

The state of water in the body. A small amount of water (4%) is bound to tissue colloids, mainly proteins and subcellular structures, membranes. This is immobilized water, or hydrated water. There is a connection between different forms of water, it can pass from one form to another.

The increase in intercellular water volume during short-term work is mainly due to blood flow, and the increase in intracellular fluid during long-term muscle work is associated with increased hydration of the proteins of the working muscles.

Regulation of water and salt metabolism

The body's water and electrolyte homeostasis is regulated by the nervous and endocrine systems. Humoral regulation is carried out mainly by antidiuretic hormone, aldosterone and atrial natriuretic hormone. The kidneys are able to change the rate of urine production within a wide range and adapt to the intake of water in the body (fig. 15.1).

Antidiuretic hormone (ADH) affects the water balance by increasing water reabsorption by the nephron tubules and decreasing diuresis. The secretion of ADH is activated by osmoreceptor stimuli in case of increased plasma osmolarity, as well as by volumetric receptors in case of decreased blood volume.

Aldosterone increases the reabsorption of sodium in the nephron tubules and retains it in the body, and also inhibits the reabsorption of potassium. Aldosterone secretion is increased by irritation of volumetric receptors with a decrease in blood volume, as well as activation of the renin-angiotensin system. Aldosterone and ADH interact closely in regulating the volume and concentration of extracellular fluid minerals.

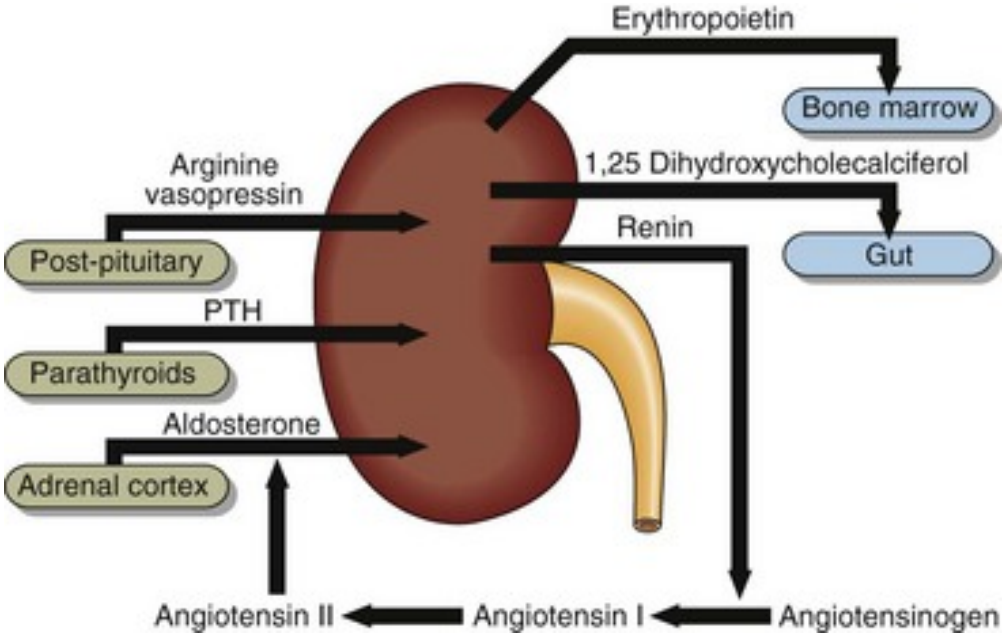


Fig. 15.1. Endocrine links in the kidney

Atrial natriuretic hormone stimulates natriuresis and is an antagonist of aldosterone. It also stimulates potassium excretion.

The juxtaglomerular nephrons of the kidney contain chemoreceptors that are sensitive to changes in plasma osmolarity. When the plasma osmolarity decreases (this occurs when the concentration of sodium cations in the plasma decreases), chemoreceptors transmit a signal to stimulate the synthesis of a special enzyme, **renin, in the** renal tissue. This enzyme catalyzes the proteolytic destruction of the angiotensinogen polypeptide entering the renal tissue from the bloodstream (80% synthesized in the liver), with the formation of a shorter **angiotensin I** polypeptide. This polypeptide is sent from the renal tissue to the bloodstream, where it undergoes limited proteolysis under the action of a special peptidyl peptidase A of the vascular endothelium, or kininase II (an enzyme of the blood kinin system) to form

angiotensin II. This polypeptide is a hormone for which receptors have been found in the adenohypophysis and posterior pituitary gland (stimulates the secretion of ACTH and vasopressin), in the endothelium of blood vessels (has a vasoconstrictor effect), in the adrenal cortex (stimulates the synthesis and secretion of aldosterone). The first and last effects of angiotensin II contribute to an increase in plasma osmolarity.

Regulation of acid-base balance

The kidneys play an important rol in maintaining acid-base homeostasis.

Depending on the nature of the diet, the acidity of urine can vary significantly (pH 5.5-7.5). The concentration of free H^+ ions in urine can be 800 times higher than their content in blood plasma. The mechanisms that maintain the URP include:

1. Acidogenesis is the removal of H^+ ions in organic acids. CO_2 through its hydrated form - carbonic acid - becomes a source of H^+ ions in the body:

$$H_2O + CO_2 = H_2CO_3 = H^+ + HCO_3^-$$

H^+ ions interact with organic acid salts:

$$CH_3COONa + H^+ = Na^+ + CH_3COOH$$

The resulting sodium bicarbonate is returned to the bloodstream and regenerates the bicarbonate buffer:

$$Na^+ + HCO_3^- = NaHCO_3$$

2. Conversion of dibasic phosphate to monobasic phosphate:

$$Na_2HPO_4 = 2Na^+ + HPO_4^-$$

$$H^+ + NaHPO_4^- = NaH_2PO_4$$

3. Formation and excretion of ammonium salts (ammoniogenesis).

The source of ammonia is the deamination of glutamine (the transport form of ammonia):

$$\text{Glutamine} = \text{glutamic acid} + NH_3$$

$$NH_3 + H^+ = NH_4^+$$

$$NaCl = Na^+ + Cl^-$$

$$NH_4^+ + Cl^- = NH_4Cl$$

The sodium released in the above reactions after interaction with carbon dioxide replenishes the plasma bicarbonate buffer.

Thus, sodium ions are exchanged for hydrogen ions through specific energy-dependent transport mechanisms. The secretion of hydrogen ions depends on carbon dioxide tension, glutamine content, glutaminase activity, renal blood flow, etc.

Physical and chemical properties of urine

Urine is an aqueous solution that contains about 200 chemical ingredients, among which there are physiological and pathological, threshold and non-threshold.

In total, about 60 g of substances are excreted in the urine of an adult per day, of which 35-45 g are organic and 15-25 g are mineral.

1. The volume of daily urine:

Children:

- newborns on the first day of life - 21 ml;
- 1 month - 320 ml;
- 1 - 2 years - 450 ml;
- 2 - 5 years - 520 ml;
- 5 - 8 years - 680 ml;
- 8 - 11 years old - 850 ml;
- 11 - 18 years - 1,000 - 1,100 ml;
- Adults - 1,500-1,800 ml.

Urine output over a certain period of time (during the day, night, or the whole day) is called **diuresis**.

Polyuria - increased urine output of more than 2 liters per day - is observed in diabetes mellitus and diabetes insipidus, nervous diseases, kidney disease, after taking diuretics and some cardiac medications.

Oliguria - a decrease in the amount of urine to 500 ml or less - is observed in case of kidney inflammation, heart disease, fever, frequent diarrhea, vomiting, profuse sweating, edema due to circulatory failure.

Anuria - absence of urine or urine output of up to 50 ml per day - occurs in case of severe impairment of the excretory function of the kidneys (uremic condition), blockage of ureters, mercury, lead, arsenic poisoning.

2. The color of the urine.

Normally, an adult's urine is straw yellow due to pigments such as urochrome, urobilin, and uroerythrin. In newborns, urine is almost colorless. Low-density urine can be almost colorless, and high-density urine can be the color of strong tea. Impurities of blood or hemoglobin give the urine a red or brown color. Urates color urine orange, and it becomes black in melanoma and alkaptonuria. Indica turns it blue-green. Milky white color is observed in chyluria, high lipid and phosphate content. After eating beets, carrots, strawberries, urine is colored by the pigments of these products.

3. Transparency of urine.

Freshly passed urine is normally clear. Urine turbidity can be the result of the presence of red blood cells, white blood cells, epithelium, bacteria, fat droplets, precipitation of salts, which depends on their concentration, pH, mucus, and urine storage temperature (low temperature promotes salt precipitation).

4. Urine reaction:

Normally, the urine reaction is predominantly slightly acidic. Urine pH in adults can range from 5.2 to 6.8.

An acidic urine *reaction* (pH < 5.0) is observed:

- under physiological conditions (overload with meat products);
- in case of respiratory and metabolic acidosis (diabetic coma, heart failure, AKI);
- in case of acute nephritis;
- for gout;
- in case of kidney tuberculosis;
- in hypokalemia (due to increased ion excretion to maintain ionic balance);
- as a result of the action of ascorbic acid, corticotropin, ammonium chloride;

- in case of fever;
- in case of urolithiasis.

The alkaline reaction of urine (pH>7.0) is observed in:

- eating plant-based foods;
- metabolic and respiratory alkalosis (increased acidity of gastric juice, after severe acidic vomiting, during the resorption of edema);
- active inflammatory processes in the urinary tract;
- hyperkalemia;
- chronic renal failure;
- during the resorption of edema;
- hyperparathyroidism;
- as a result of the action of sodium citrate, bicarbonates, adrenaline, aldosterone.

5. Specific gravity

This urine indicator characterizes the concentration function of the kidneys.

The norm for children aged 1 - 10 days is 1.008 - 1.018; 2 - 3 years - 1.01 - 1.017; 4 - 5 years - 1.012 - 1.02; 10 - 12 years - 1.01 - 1.025. In adults - 1.008 - 1.030.

Hyperstenuria - increased density - is observed in fever-like conditions, some kidney diseases, diabetes mellitus, vomiting, diarrhea. Low density - **hyposthenuria** - occurs in severe renal dysfunction, diabetes mellitus, nervous diseases, polyuria. **Isostenuria is** when the density of urine is low and almost the same throughout the day. This is a characteristic sign of chronic renal failure.

Chemical composition of urine

Urine contains many end products of metabolism. Among them are organic and inorganic substances. Among the organic components, the main one is **urea,** which makes up about 4/5 of the total urinary nitrogen. The daily excretion of urea in an adult can range from 12 to 36 g and depends on the nature of the diet. The more

protein a person consumes, the higher the concentration of urea in the urine. Increased urinary excretion of urea is characteristic of intensive protein breakdown (shock states, fever, cancer, burns). A decrease in urea excretion is observed primarily in case of impaired urea synthesis due to liver failure, as well as in case of decreased renal nitrogen excretory function.

Uric acid is the end product of purine base metabolism. The daily urinary excretion of uric acid is 0.5-1.0 g and depends on the nature of the diet. Excessive consumption of foods rich in purine bases (brain, liver, kidneys, cocoa, coffee, legumes) leads to increased urinary excretion of uric acid. A significant increase in uric acid excretion is observed in case of increased nucleoprotein breakdown (burn disease, radiation sickness, leukemia), as well as in gout. The latter is characterized by an increase in the content of uric acid in the blood - hyperuricemia, which is accompanied by the deposition of crystals of its salts - urates in the joints and cartilage, the development of inflammation, pain and deformation.

Creatinine is the end product of creatine metabolism. The daily urinary excretion of creatinine is 1.0-2.0 g and depends on muscle mass. Liver and kidney diseases, muscle atrophy cause a decrease in creatinine excretion. Intense physical activity, increased protein breakdown in infectious diseases, and intoxication increase creatinine excretion.

Urinary excretion of **amino acids** and short peptides is about 3.0 g per day. Increased protein breakdown in tissues (extensive trauma, shock, starvation, radiation sickness, acute pancreatitis, sepsis) leads to increased urinary excretion of amino acids - hyperaminoaciduria. A decrease in the biosynthesis of plasma proteins in the liver in case of liver failure is also accompanied by increased urinary excretion of amino acids.

Indocane is a product of indole neutralization, which is formed as a result of protein decay in the intestine. The daily urinary excretion of indocan is 5-25 mg.
Urine excretes small amounts of organic acids, neutral fats, and cholesterol. Urine contains vitamins, most of which are water-soluble (C, B , B12 , B6 , PP).

Urinary hormone excretion is often studied to assess endocrine gland function, in particular, 17-ketosteroids, 17-oxycorticosteroids are indicators of steroid hormone metabolism, and therefore, in steroid diabetes mellitus, which occurs as a result of excessive levels of adrenal cortical hormones - corticosteroids - in the blood, their urinary excretion increases. Endocrine dysfunction is accompanied by changes in the excretion of hormones and their catabolic products in the urine.

Among urinary enzymes, the activity of alpha-amylase, lipase, proteolytic enzymes, in particular trypsin, pepsin, is widely used to assess the state of the pancreas and the acid-forming function of the stomach. Pancreatic damage is accompanied by an increase in the content of pancreatic enzymes (alpha-amylase, lipase, proteinase), which is a diagnostic criterion for acute pancreatitis.

Determination of protein, glucose, ketone bodies and bile pigments in urine

In a healthy person, protein in the urine is practically undetectable (up to 0.033 g/l) or absent altogether.

Proteinuria is the appearance of protein in the urine in concentrations that make it possible to detect it by qualitative methods:

- Physiological (after exercise, emotional, cold, intoxication, orthostatic);
- Pathological (pre-renal, real, post-renal):

A. *Prerenal* (myeloma, muscle necrosis, erythrocyte hemolysis). It develops in the presence of an unusually high plasma concentration of low molecular weight protein filtered by normal glomeruli in an amount exceeding the physiological capacity of the tubules for reabsorption.

B. Renal :

- glomerular (glomerulonephritis, hypertension, exposure to infectious and allergic factors, decompensation of cardiac activity) is caused by damage to the glomerular filter;

- tubular (amyloidosis, acute tubular necrosis, interstitial nephritis, Fanconi syndrome) occurs due to the inability of the tubules to reabsorb plasma low molecular weight proteins that have passed through an unchanged glomerular filter.

C. *Postrenal* (in cystitis, urethritis, colpitis) is caused by damage to the glomerular filter or dysfunction of the convoluted renal tubule epithelium.

Glucosuria - urinary glucose excretion Normally, glucose is completely reabsorbed in the proximal tubules and its excretion per day does not exceed 130 mg. Glucosuria occurs in hyperglycemia that exceeds the renal threshold (9.0 - 10.0 mmol/l). It is most common in diabetes mellitus, as well as in case of emotional stress, in case of hereditary deficiency of enzymes that provide glucose reabsorption, in case of severe renal failure.

The excretion of **ketone** bodies in the urine - **ketonuria** - occurs in lipid metabolism disorders that contribute to excessive synthesis of ketone bodies and the development of ketosis (diabetes mellitus, fasting, fever, thyrotoxicosis).

The appearance of direct bilirubin in the urine - **bilirubinuria** - is observed in case of impaired bile flow (obstructive jaundice), damage to hepatocytes (hepatocellular jaundice), as direct bilirubin passes through the renal filter. Urobilin in the urine - **urobilinuria - appears in case of** liver damage (hepatitis, cirrhosis), when hepatocyte urobilinogen uptake is impaired.

Hyperaminoaciduria - the excretion of amino acids in the urine - is an important diagnostic indicator of various diseases, as the normal content of amino acids in the urine is insignificant. Maple *syrup disease* (branched-chain ketoaciduria or leucinosis) is an autosomal recessive disease caused by a disorder of the metabolism of branched-chain amino acids (leucine, isoleucine, and valine). *Alkaptonuria is a* hereditary disease caused by a genetically determined deficiency of the enzyme homoanthine oxidase, an intermediate product of phenylalanine and tyrosine metabolism, resulting in the accumulation of homoanthine acid in the blood and urine. A characteristic sign of the disease deficiency is the black color of the diapers, because homogenous acid is oxidized in the air and then polymerized into a melanin-like compound.

Porphyrins in the urine - **porphyrinuria** - occurs in liver disease, certain types of anemia, lead poisoning, and can also be hereditary.

2. TASKS FOR INDEPENDENT WORK.

In the table with the test tasks, underline the key words, select the correct answer and justify it:

1.	A 50-year-old patient complains of thirst, drinks a lot of water, and has severe polyuria. Blood glucose is 4.8 mmol/L, there is no glucosuria and ketonemia, urine is colorless, specific gravity is 1.002-1.004. What is the cause of polyuria? A. Aldosteronism B. Insulin deficiency C. Lack of vasopressin D. Hypothyroidism E. Thyrotoxicosis	
2.	A patient with a suspected diagnosis of progressive muscular dystrophy was tested for urine. The presence of which compound in the urine confirms the diagnosis? A. Creatinine B. Myoglobin C. Collagen D. Creatine E. Calmodulin	
3.	A person has a blood glucose level of 15 mmol/l (reabsorption threshold is	

	10 mmol/l). The consequence of this will be: A. Decrease in diuresis B. Reduced secretion of vasopressin C.Reduced secretion of aldosterone D. Reduction of glucose reabsorption E. Glucosuria	
4.	A two-year-old child with mental and physical retardation, who suffers from frequent vomiting after eating, was brought to the hospital. Phenylpyruvic acid was found in the urine. What metabolic disorder is the consequence of this pathology? A. Lipid metabolism B. Amino acid metabolism C. Carbohydrate metabolism D. Water-salt metabolism E. Phosphorus-calcium metabolism	
5.	A 13-year-old boy complains of general weakness, dizziness, fatigue. There is a lag in mental development. The examination revealed a high concentration of valine, isoleucine, leucine in the blood and urine. Urine has a specific odor. What is the most likely diagnosis?	

	A. Maple syrup disease B. Histidinemia C. Tyrosinosis D. Basement membrane disease E. Addison's disease	
6.	The infant has coloration of the sclerae and mucous membranes. Urine, darkening in the air. Homogentisic acid is found in the blood and urine. What can be the cause of this condition? A. Cystinuria B. Histidinemia C. Alkaptonuria D. Galactosemia E. Albinism	
7.	A 52-year-old patient for the past few days has been experiencing pain in the right after eating fatty foods. Visually, yellowing of the sclerae and skin, acholic feces, and "beer-colored" urine are detected. What substance in the patient's urine causes the dark color of the urine in case of obtundative jaundice? A. Ketone bodies B. Glucose	

	C. Stercobilin D. Urobilin E. Bilirubin glucuronide	
8.	The patient has hypersensitivity of the skin to sunlight. His urine becomes dark red in color after standing for a long time. What is the most likely cause of this condition? A. Porphyria B. Alkaptonuria C. Albinism D. Pelagra E. Hemolytic jaundice	
9.	A 65-year-old man with gout complains of pain in the kidneys. Ultrasound examination revealed the presence of kidney stones. An increase in the concentration of which substance is the most likely cause of stone formation in this case? A. Uric acid B. Cholesterol C. Urea D. Bilirubin E. Cystine	
10.	A patient complained of constant thirst. Hyperglycemia, polyuria and	

	increased content of 17-ketosteroids in the urine were detected. Which disease is most likely? A. Addison's disease B. Myxedema C. Glycogenosis type I D. Steroid diabetes mellitus E. Insulin-dependent diabetes mellitus	
11.	A 58-year-old man has a clinical picture of acute pancreatitis. Increase in urine of which of the following substances will confirm the third diagnosis? A. Urea B. Residual nitrogen C. Albumin D. Amylase E. Uric acid	
12.	A woman with primary hyperparathyroidism has recurrent attacks of renal colic. Ultrasound examination revealed the presence of small kidney stones. What is the most likely cause of these stones?	

	A. Hyperkalemia B. Hyperuricemia C. Hypercalcemia D. Hyperphosphatemia E. Hypercholesterolemia	
13.	The patient complains of shortness of breath after exercise. Objectively: anemia, the presence of paraprotein in the gamma globulin zone. Which urine test should be performed to confirm the diagnosis of myeloma? A. Bence-Jones protein B. Hemoglobin C. Bilirubin D. Antitrypsin E. Ceruloplasmin	
14.	A patient who complains of polyuria and polydipsia, found sugar in the urine. Plasma sugar content is normal. What is the mechanism of glucosuria in the patient? A. Impaired glucose reabsorption in the nephron tubules B. Impaired glucose filtration in the glomerular department of the nephron C. Insulin resistance of cell receptors	

	D. Hyperproduction of glucocorticoids by the glands E. Insufficient production of insulin by the pancreas	
15.	A patient suffering from chronic hepatitis was loaded with sodium benzoate to assess the neutralizing function of the liver. The excretion of which substance in the urine is used to assess the neutralizing function of the liver? A. Phenylacetic acid B. Citric acid C. Oxalic acid D. Valeric acid E. Hypuric acid	

3. <u>LITERATURE: See page 320.</u>

LESSON №16

16. TOPIC: THE INTEGRATION OF METABOLIC PATHWAYS. GENERAL PRINCIPLES OF METABOLISM REGULATION

1. INFORMATION MATERIAL.

1. Key Metabolites of Carbohydrate Metabolism and Their Use in Lipid and Amino Acid Metabolism

The main intermediate metabolites of carbohydrate metabolism are **acetyl-CoA, NADPH, and pyruvate**, which play a crucial role in lipid and amino acid biosynthesis.

- **Acetyl-CoA** – a key metabolite formed from pyruvate (glycolysis), fatty acids (β-oxidation), and some amino acids.
  - Used in **fatty acid synthesis** (via malonyl-CoA), cholesterol synthesis, and ketone body production.
  - Enters the **Krebs cycle** to generate energy (ATP).
- **NADPH** – an essential reducing agent in many anabolic processes:
  - Required for **fatty acid synthesis** (used in acetyl-CoA carboxylase and fatty acid synthase reactions).
  - Plays a role in antioxidant defense (glutathione reduction).
- **Pyruvate** – a central metabolite linking carbohydrate metabolism with lipids and amino acids:
  - Converts to **acetyl-CoA** (for energy and synthetic processes).
  - Participates in **gluconeogenesis** (via oxaloacetate).
  - Can be a **substrate for alanine synthesis** (transamination) and other amino acids.

2. Krebs Cycle Metabolites as Intermediates in Carbohydrate, Lipid, and Amino Acid Metabolism

The Krebs cycle not only generates energy but also provides intermediates for other metabolic pathways:

- **Citrate** – used in fatty acid and cholesterol synthesis.

- **Oxaloacetate** – an intermediate in gluconeogenesis and a precursor for aspartate (a substrate for purine and pyrimidine synthesis).
- **α-Ketoglutarate** – involved in amino acid synthesis (glutamate, glutamine).
- **Succinyl-CoA** – used in heme biosynthesis.
- **Fumarate and malate** – involved in gluconeogenesis.

Thus, the Krebs cycle integrates carbohydrate, lipid, and amino acid metabolism.

3. Use of Nucleoside Triphosphates in Carbohydrate, Lipid, and Amino Acid Metabolism

Nucleoside triphosphates (ATP, UTP, GTP, CTP) have specific functions in metabolism:

- **ATP** – the main energy source for:
  - Glucose activation in glycolysis (glucokinase/hexokinase).
  - Glycogen synthesis (glucose-1-phosphate → UDP-glucose).
  - Protein biosynthesis (amino acid activation, polypeptide chain elongation).
  - Fatty acid synthesis (used for acetyl-CoA carboxylation).
- **GTP** – used in gluconeogenesis (conversion of oxaloacetate to phosphoenolpyruvate) and protein translation.
- **UTP** – participates in glycogen synthesis (UDP-glucose as a glucose donor).
- **CTP** – required for phospholipid biosynthesis.

4. ATP/ADP Ratio as a Key Factor in Controlling the Duration of Catabolic and Anabolic Pathways

The ATP/ADP ratio determines the direction of metabolic pathways:

- **High ATP/ADP ratio** (energy surplus):
  - Inhibits catabolic processes (glycolysis, fatty acid β-oxidation, Krebs cycle).
  - Activates anabolic processes (fatty acid synthesis, glycogenesis).
- **Low ATP/ADP ratio** (energy deficit):
  - Stimulates catabolism (glycolysis, glycogen breakdown, β-oxidation, Krebs cycle).
  - Suppresses anabolic processes.

This regulatory mechanism ensures the cell's energy balance.

5. Hormonal Regulation of Key Metabolites

Hormones coordinate the use of acetyl-CoA, NADH, and NADPH in different pathways:

- **Insulin** (an anabolic hormone):
  - Stimulates **glycolysis** (via phosphofructokinase-2 activation).
  - Enhances **fatty acid synthesis** (by activating acetyl-CoA carboxylase).
  - Inhibits **gluconeogenesis and lipolysis**.
- **Glucagon** (a catabolic hormone):
  - Activates **gluconeogenesis and glycogenolysis**.
  - Enhances **lipolysis** (via hormone-sensitive lipase activation).
- **Adrenaline** (a stress hormone):
  - Stimulates **glycogen breakdown in the liver and muscles**.
  - Increases **lipolysis** for energy production.
- **Cortisol** (a long-term stress hormone):
  - Activates **gluconeogenesis**.
  - Promotes **proteolysis** (protein breakdown into amino acids).
  - Enhances **lipolysis**.
- **Thyroid hormones (T3 and T4)**:
  - Increase ATP production by stimulating mitochondrial metabolism.
  - Stimulate **lipolysis and gluconeogenesis**.

Thus, hormones ensure a balance between the body's energy needs and the utilization of key metabolites.

These mechanisms are fundamental for understanding metabolism and its regulation under normal and pathological conditions.

2. TASKS FOR INDEPENDENT WORK.

In the table with the test tasks, underline the key words, select the correct answer and justify it:

1.	ATP is considered as energy source for a lot of synthesises in a cell. Point	

	out the main important process of its formation in humans: A. Synthesis of ATP from GTP B. Oxidative phosphorylation C. Substrate phosphorylation D. Synthesis of ATP from UTP E. Creatine phosphate kinase reaction	
2.	This metabolite is formed in catabolic pathway from glucose and then is used for some lipids synthesis. Name it: A. Pyruvic acid B. Acetyl - CoA C. Phosphoenolpyruvate D. Lactate E. Oxaloacetate	
3.	This metabolite is formed in Pentose Phosphate cycle and then is used for some lipids synthesis. Name it: A. Malate B. Acetyl-CoA C. NADPH D. NADH E. Ribose-5-phosphate	

4.	This vitamin deficiency causes the accumulation of free high fatty acids and the infringement of all processes that they are involved in the liver. Name this vitamin: A. Rutin B. Pantothenic acid C. Pyruvic acid D. Lactic acid E. Ascorbic acid	
5.	Name the process that is inhibited after lipolysis stimulation in the liver: A. Synthesis of glycogen B. Pentose Phosphate Cycle C. Glycolysis D. Transamination of amino acids E. Beta-oxidation of high fatty acids	
6.		

	Name the process that is not stimulated by insulin in the target tissues: A. Synthesis of glycogen B. Oxidative decarboxylation of pyruvate C. Glycolysis D. Krebs cycle E. Beta-oxidation of high fatty acids	
7.	Name the process that is stimulated in the liver of patient under poinsoning by some xenobiotics: A. Glycogenesis B. Pentose phosphate cycle C. Glycolysis D. Krebs cycle E. Ketone bodies synthesis	
8.	Name the metabolite used for formation of all steroids in humans: A. Pyruvic acid B. Cholesterol C. Aldosterone D. High fatty acid	

	E. Oxaloacetate	
9.	Name the process that is stimulated in the liver cell at the ratio ATP/ADP>1: A. Glycogenesis B. Pentose phosphate cycle C. Glycolysis D. Krebs cycle E. Oxidation of high fatty acids	
10.	10. Name the process that is stimulated in the liver by glucagon: A. Glycogenesis B. Glycogenolysis C. Glycolysis D. Krebs cycle E. Cholesterol degradation	

3. <u>LITERATURE: See page 320.</u>

17. TOPIC: BORDER CONTROL FROM SECTION 2.

2. OBJECTIVES:

Determine the level of students' mastery of the material of all sections included in Section 2 based on test results.

3. TASKS FOR INDEPENDENT WORK IN PREPARATION FOR THE MILESTONE TEST FROM SECTION 2:

3.1. LIST OF THEORETICAL ISSUES

Core topic 6.

Metabolism of chromoproteins and nucleoproteins. Fundamentals of molecular biology and genetics

1. Porphyrin metabolism: structure of heme; reaction scheme of protoporphyrin IX and heme biosynthesis.

2. Hereditary disorders of porphyrin biosynthesis, types of porphyrias.

3. Hemoglobin and heme catabolism (diagram); formation and structure of bile pigments.

4. Pathobiochemistry and types of jaundice; biochemical diagnosis of jaundice.

5. Nitrogenous bases, nucleosides and nucleotides. Structure and biological role.

6. Free nucleotides and their derivatives (ATP, GTP, UTP, CPP, NAD, NADP, FAD, FMN, c-AMP, c-GMP) - structure and function.

7. Biosynthesis of purine nucleotides: reaction scheme, regulation of the process.

8. Biosynthesis of purine nucleotides: reaction scheme, regulation of the process.

9. Biosynthesis of deoxyribonucleotides: reaction scheme, regulation of the process.

10. Catabolism of purine nucleotides. Disorders of purine metabolism. Gout .

11. Catalysis of pyrimidine nucleotides. End products of their decomposition.

12. Nucleoproteins: structure, biological functions, classification.

13. Molecular organization of eukaryotic nuclear chromatin: nucleosomes, histones and non-histone proteins.

14. Nucleic acids. Comparative characteristics of DNA and differences in RNA types: structural features (primary, secondary, tertiary structures, Watson-Crick model, Chargeoff's rules), localization, functions.

15. Molecular mechanisms of DNA replication. Types of replication. Stages and enzymes of DNA replication in pro- and eukaryotes.

16. General characteristics and types of mutations. Mechanisms of action of mutagens. Mechanisms of DNA repair. The concept of molecular diseases, hereditary diseases and enzymopathies. Genetic engineering.

17. Modern ideas about the mechanism of transcription. RNA polymerases of pro- and eukaryotes. Transcription signals. Post-transcriptional processing of m-RNA in eukaryotes.

18. Biochemical composition, structure and function of biological membranes. Liquid mosaic model and asymmetry of membranes. The role of lipids in their composition.

19. Genetic code and its properties.

20. The ribosomal protein synthesizing system of the cell.

21. The role of m-RNA, t-RNA and r-RNA in protein biosynthesis.

22. The mechanism of translation and its stages: initiation, elongation and termination. Factors of initiation, elongation and termination in pro- and eukaryotes.

23. Activation of amino acids: mechanism, role of aminoacyl-tRNA synthetase.

24. Energy supply of protein synthesis. Post-translational processing. Regulation of translation.

25. Modern concepts of intracellular regulation of prokaryotic gene expression (F. Jacob and J. Mono operon hypothesis). The concept of the mechanism of gene induction and repression.

26. Antibiotics - inhibitors of various stages of protein biosynthesis: inhibitors of initiation (streptomycin, rifamycin), elongation (erythromycin, chloramphenicol, tetracycline, cycloheximide, puromycin) and termination (lincomycin, amicetin, erythromycin, chloramphenicol, streptomycin).

Core topic 7.

Molecular mechanisms of hormone action

1. Hormones: general characteristics, structure, properties, modern research methods. The role of hormones and other bioregulators in ensuring intercellular integration of human body functions.

2. Classification of hormones. Correlation of structure and mechanism of action of hormones.

3. The concept of hormone target organs and cells. Types of receptors: features of structure and localization in the cell. Membrane (ionotropic, metabotropic) and cytosolic receptors.

4. Interrelation and regulation of hormone secretion. Principles of direct and feedback, long and short feedback chains.

5. Biochemical systems of intracellular transmission of hormonal signals: G-proteins, secondary mediators (c-AMP, calcium/calmodulin, IP_3, DAG, phospholipase C), protein kinases.

6. Membrane mechanism of action of protein-peptide hormones.

7. Membrane-intracellular mechanism of hormone action. Functions of the components of the system of hormone signal transmission to the cell.

8. Cytosolic mechanism of action of lipophilic (steroid and thyroid) hormones.

9. Hypothalamic hormones - liberins and statins: peculiarities of structure, secretion and effect on the pituitary gland.

10. Neuropeptides (vasopressin, oxytocin): structure, synthesis and secretion, functions. Diabetes insipidus.

11. Hormones of the anterior pituitary gland: chemical nature, regulation of secretion, effect on metabolism. Pathological processes associated with disorders of their synthesis

12. Pituitary hormones are products of post-translational processing of proopiomelanocortin. Chemical structure and effect on metabolism. Pathological processes associated with disorders of their synthesis.

13. Adrenal cortical hormones (C21-steroids) - GCS and mineralocorticoids. Structure, effect on metabolism. Pathological processes associated with disorders of their synthesis.

14. Catecholamines. Structure, effect on metabolism. Pathological processes associated with disorders of their synthesis.

15. Female sex hormones (estrogen, progesterone): structure, effect on metabolism, regulation of secretion depending on the phase of the ovulation cycle.

16. Male sex hormones (androgens): structure, effect on metabolism.

17. Thyroid hormones: structure, effect on metabolism. Hypo- and hyperthyroidism.

18. Pancreatic hormones (insulin, glucagon). Structure, effect on metabolism. Pathological processes associated with disorders of their synthesis. Growth-stimulating effects of insulin.

19. Hormonal regulation of calcium homeostasis: Parathyroid hormone, calcitonin, calcitriol. Structure, regulation of secretion, effect on target tissues. Features of calcium and phosphate metabolism with changes in their concentration.

20. Eicosanoids (prostaglandins, prostacyclins, thromboxanes, leukotrienes). Structure, effects. Drugs - regulators of their metabolism.

21. Mediators and hormones of the immune system (cytokines, interferons): chemical nature, synthesis, effects.

Core topic 8.

Biochemistry of vitamins

1. Biological role and classification of vitamins.

2. Features of absorption of water-soluble vitamins in the gastrointestinal tract. Exo- and endogenous causes of vitamin deficiency. Avitaminosis.

3. Features of absorption of fat-soluble vitamins in the gastrointestinal tract. The concept of hypervitaminosis.

4. Vitamins B1, B2, B3, B5 (PP), B6, B9 (Nd), B12, H: structure of coenzymes (prosthetic groups), mechanism of action, daily requirement, sources. Manifestations of deficiency.

5. Vitamins C and P: structure, participation in metabolism, daily requirement, sources. Manifestations of deficiency.

6. Vitamin-like substances. The role of carnitine, ubiquinone and lipoic acid in metabolism.

7. Vitamins of group A and carotenes: structure, participation in metabolism, daily requirement, sources. Manifestations of hypo- and hypervitaminosis.

8. Vitamins of group E: structure, participation in metabolism, daily requirement, sources. Manifestations of deficiency.

9. Vitamins of group D: structure, participation in metabolism, daily requirement, sources. Manifestations of hypo- and hypervitaminosis.

10. Vitamins of group K: structure, participation in metabolism, daily requirement, sources. Vitamin K analogues and antagonists as non-proprietary drugs.

11. Vitamin F (complex of polyunsaturated higher fatty acids): structure, participation in metabolism, daily requirement, sources. Manifestations of deficiency

12. The use of vitamin preparations in the prevention and treatment of diseases. The concept of antivitamins and mechanisms of their action.

Core topic 9.

Functional biochemistry of organs and tissues

1. General characteristics of the chemical composition of muscle tissue. Proteins of sarcoplasm, myofibrils and stroma. Non-protein nitrogenous and nitrogen-free substances of muscles.

2. Molecular mechanisms of muscle contraction. The role of calcium ions.

3. Pathways of ATP synthesis in different muscle types. Synthesis and role of creatine phosphate in the energy supply of muscle contraction. Creatinine.

4. Biochemical blood parameters in the diagnosis of myocardial infarction and myopathy.

5. General concepts of the chemical composition of connective tissue. Proteins (collagen, elastin, proteoglycans, glycoproteins) and heteropolysaccharides of connective tissue.

6. Disorders of metabolism in connective tissue. Mucopolysaccharidoses and collagenoses.

7. Chemical composition and biochemical functions of blood.

8. Clinical and biochemical characteristics of the main fractions of plasma and serum proteins. The concept of hypo-, hyper-, para- and dysproteinemia.

9. Clinical and biochemical characteristics of transport proteins, acute phase proteins and proteolysis inhibitors.

10. Classification of plasma enzymes, their use in the diagnosis of diseases.

12. Clinical and biochemical characteristics of the main non-protein nitrogen-free plasma components.

13. Mineral composition of blood plasma. Methods of determination, clinical and diagnostic value.

14. Acid-base balance and its disorders, types and mechanisms of acidosis and alkalosis. Buffer systems of blood.

15. The role of the liver in carbohydrate metabolism.

16. The role of the liver in protein metabolism.

17. The role of the liver in the regulation of blood lipid composition.

18. Urine-forming function of the liver.

19. Bile-forming functions of the liver.

20. The role of the liver in the metabolism of bile pigments.

21. Conjugation reactions in hepatocytes: biochemical mechanisms, functional significance.

22. Microsomal oxidation reactions. Cytochrome P450; electron transport chains in the membranes of hepatocytes.

23. Detoxification function of the liver; types of biotransformation reactions of xenobiotics and endogenous toxins.

24. Definition, classification and biological role of xenobiotics, ways of their intake, biotransformation and excretion from the body.

25. Liver dysfunction in pathologies. Liver tests.

26. Structure of bone tissue and teeth.

27. Mechanisms of bone and tooth mineralization.

28. Disorders of bone metabolism. Biochemical tests for the assessment of disorders. Ways of metabolic correction of osteoporosis.

29. The structure and characteristics of enamel metabolism.

30. Structure and peculiarities of metabolism in dentin and cement.

31. Chemical composition, physical properties and biological role of saliva.

32. Mechanisms and regulation of saliva secretion. Types of disorders.

33. Biochemical studies of saliva in the diagnosis of diseases of the oral cavity.

34. Hormonal regulation of oral cavity metabolism.

35. Clinical and biochemical characteristics of gingival, gingival and oral fluids.

36. Biochemical mechanisms of caries development. Principles of prevention and treatment.

37. Biochemical mechanisms of periodontitis development. Principles of prevention and treatment.

38. Biochemical mechanisms of development of sialoadenitis and sialosis. Principles of prevention and treatment.

3. LITERATURE. See page 320.

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