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PRINCIPLES OF METABOLITHOTROPIC THERAPY IN PEDIATRIC PRACTICE. CLINICAL AND PHARMACOLOGICAL CHARACTERISTICS OF MODERN METABOLITHOTROPIC AGENTS (PART 1)

In the article, the authors, based on their own research, as well as based on the results of other scientists, gave an idea of such concepts as metabolitotropic therapy and metabolic and metabolitotropic drugs, their place in the basic therapy of diseases, the cardiovascular system, the central nervous system, the hepatobiliary system, etc. The authors provided a classification of metabolitotropic agents depending on their chemical structure and mechanism of action. The general principle of action of metabolitotropic agents is described. Molecular and biochemical mechanisms of energizing, antioxidant, neuroprotective, stress-protective, cardioprotective action of arachidonic acid, liposomes, magnesium preparations, mexidol, L-lysine, L-carnitine and taurine are described in detail. The article provides an experimental rationale for the use of metabolitotropic agents in neonatology and pediatrics.

***Key words:** metabolic and metabolitotropic drugs, classification, preparations of magnesium, arachidonic acid, taurine, L-lysine, L-carnitine.*

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ПРИНЦИПИ МЕТАБОЛІТОТРОПНОЇ ТЕРАПІЇ У ПЕДІАТРИЧНІЙ ПРАКТИЦІ. КЛІНІКО-ФАРМАКОЛОГІЧНА ХАРАКТЕРИСТИКА СУЧАСНИХ МЕТАБОЛІТОТРОПНИХ ЗАСОБІВ (ЧАСТИНА 1)

У статті автори на підставі власних досліджень, а також базуючись на результатах інших учених, дали уявлення про такі поняття, як «метаболітотропна терапія» та «метаболітні та метаболітотропні лікарські засоби», їхнє місце у базовій терапії захворювань, серцево-судинної системи, ЦНС, гепатобіліарної системи тощо. Надано класифікацію метаболітотропних засобів залежно від їхньої хімічної структури та механізму дії. Описано загальний принцип дії метаболітотропних засобів. Докладно описано молекулярні та біохімічні механізми енерготропної, антиоксидантної, нейропротективної, стреспротективної, кардіопротективної дії арахідонової кислоти, ліпосом, препаратів магнію, мексидолу, L-лізину, L-карнітину та таурину. Надано експериментальне обґрунтування застосування метаболітотропних засобів у неонатології та педіатрії. Описано особливості призначення цих препаратів у педіатричній практиці: показання до застосування, особливості дозування та можливі побічні реакції.

***Ключові слова:** метаболітні та метаболітотропні лікарські засоби, класифікація, препарати магнію, арахідонової кислоти, таурину, L-лізину, L-карнітину.*

1.1. General principles of action of metabolitotropic agents

At the end of the 20th and at the beginning of the 21st century, the attention of clinicians began to attract metabolic drugs that are structurally similar to the components of the body and metabolitotropic agents that mainly affect metabolism (Galenko-Yaroshevsky et al., 2001).

In most of these metabolitotropic drugs, there is only a slight interval between the observation of fluctuations in metabolism and a change in the function of the myocardium, liver, and nervous system. Thus, these drugs, affecting the above-mentioned organs and systems, can have cardio-, neuro- and hepatotropic effects. In some metabolite drugs, the protective effect on vital systems and organs is manifested equally, in others, the effect on one substrate prevails. Some metabolic and metabolitotropic drugs also affect the immune system and hematopoiesis.

Metabolic neuroprotectors can be included in the pharmacotherapy of a wide range of diseases of the central nervous system, starting with reducing the manifestations of chronic fatigue, asthenia, memory impairment, and in the treatment of patients with alcohol and drug addiction, as a result of the toxic effect of xenobiotics, ionizing radiation, and ischemia phenomena brain, prestroke conditions with moderate cerebral insufficiency, including age-related. To increase the resistance of brain tissue against the influence of chemical and physical factors, especially in hypoxia and hypoxia of the brain, those biochemical pathways that are indicated in the methodological recommendations of the State Expert Center of the Ministry of Health of Ukraine should be regulated.

The concept of «metabolic therapy» in a broad sense includes a directed influence on the metabolism in cells and tissues by natural mediators of nervous and humoral regulation of metabolism, the metabolites themselves and their analogues. In terms of the rational classification of drugs of this type of action, it is worth noting their division into means of regulating metabolism, which realize their effect through mediators, and drugs identical or close in structure to biosubstrates – permanent participants in metabolism. The last group of agents that affect energy and plastic exchange in membrane structures, cytoplasm and organelles of the cell at the molecular level, and can be designated as metabolites and their analogues. These include metabolic products that are substrates of energy exchange and synthesis of cell structural elements or regulators of these processes.

1.2. Basic aspects of the use of metabolites in pharmacotherapy

There are three main directions of use of metabolites in medical practice:

• replacement therapy (introduction of a biosubstrate in case of its deficiency);

• regulation (stimulation, inhibition) of metabolism, including hereditary metabolic disorders (galactosemia, phenylketonuria, etc.);

• use of metabolites for selective delivery of the active component of the drug (conductor function), modification of its pharmacokinetics or reduction of toxicity.

Replacement therapy provides replenishment of the lack of metabolites necessary for energy and plastic metabolism of the cell, although many of the metabolite compounds have not become drugs. In particular, during the last 10-15 years, the positive effect of glycolysis substrates (fructose-1,6-diphosphate, phosphoenolpyruvate, hexose phosphate, etc.), tricarboxylic acid cycle (succinate, malate, alpha-ketoglutarate), creatine phosphate, glutamic and aspartic amino acids and other drugs of the metabolite type (Chekman et al., 2016).

In metabolic therapy, such amino acids as methionine, cysteine, the product of its transformation, taurine, arginine, lysine, glycine, tryptophan, histidine, as well as glutamic and aspartic amino acids, gamma-aminobutyrate are widely used. Amino acid hydrolysates and mixtures are used as part of solutions for parenteral nutrition. Only L-amino acids are used for protein biosynthesis. Dextrorotatory isomers of amino acids are mostly biologically inert, and due to sharp differences in stereostructure, they cannot be included in exchange processes. There is information about the effectiveness of DL-amino acid preparations in experiments, for example, Sufan, which has cardiotonic activity, contains DL-tryptophan and L-glutamic acid.

For the synthesis of nucleic acids and contractile proteins of the myocardium, there are known attempts to use purine and pyrimidine bases, precursors and stimulators of nucleic acid synthesis (folic acid, cyanocobalamin) and means of energy supply of synthesis (ATP, CF) as a plastic material.

Enzyme cofactors are a certain group of means of replacement therapy. Coenzymes are low-molecular organic compounds, as a rule, they include heteroatoms and a system of π-bonds. There are conditionally two main functions of coenzymes:

– catalysis of substrate transformations by a specific enzyme protein, with immediate regeneration of the coenzyme (FAD, FMN, thiamine phosphate, etc.) or its participation as a cosubstrate (NADP, NAD, etc.), with subsequent regeneration of the coenzyme by another enzyme in a combined reaction;

– activation of the substrate with the formation of a reactive compound of the acetyl-coenzyme-A type and

its transfer to another enzyme system with regeneration of the coenzyme.

According to the chemical structure, coenzymes are divided into three main groups:

• coenzymes of the heterocyclic series (tetrahydrofolic acid, nucleoside phosphates and their derivatives NAD, NADO, FAD, FMN, Co-A, etc.);

• coenzymes of the aromatic structure – ubiquinone;

• coenzymes of the aliphatic series – lipoic acid, glutathione, etc.

With a number of diseases, there is a pronounced local decrease in the level of coenzymes, in connection with which, are legitimate attempts to use such coenzymes for therapeutic purposes as folic acid, cocarboxylase, cyanocobalamin, lipoic acid, etc.

Regulation of metabolism. Stimulation of metabolism can be achieved by prescribing coenzymes that metabolize accumulated products when their further transformations are complicated as a result of hypoxia or the action of other factors.

With the accumulation of ketoacids in the myocardium, it is possible to prescribe cocarboxylase to eliminate the phenomenon of local acidosis and restore the process of formation of acetyl-Co-A.

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Metabolites in the therapy of hereditary metabolic disorders.

The successes of pathobiochemistry in the study of a number of hereditary disorders of amino acid metabolism and other genetic enzymopathies (inborn errors of metabolism) in children have opened up effective possibilities for correction of metabolism in some of these diseases.

There are two aspects of palliative correction of genetic pathology of metabolism:

–increase in the activity of enzymes, decrease in their functions, which is due to the deficiency of the necessary components of the reaction medium, which occur as a result of mutational changes in recessive hereditary deficiency of phenylalanine hydroxylase, tyrosinase, homogentinase, galactose-1-phosphate-uridyltransferase and other forms of genetic enzyme deficiency;

–restriction of the introduction of materials from the outside, the utilization of which is impaired (galactose, phenylalanine) or when their further metabolism is complicated (glycogenous disease – Gierke's disease).

In recent years, the direction associated with the correction of metabolism due to biotechnological synthesis and the use of modulators of endogenous bioregulators has been intensively developing (Chekman et al., 2016). Successes in this area are associated with the discovery and detailed study of such compounds as modulators of endothelial synthesis of NO, calcitonin-gene-related peptide, calmodulin, vasoactive, intestinal polypeptide, urocortin – an endogenous polypeptide with anti-ischemic activity and a number of other biologically highly active and selectively acting peptides.

The greatest achievements of gene therapy in the field of cardiopharmacology are associated with the use of angiogenesis stimulation factors in the area of development of intercoronary anastomoses.

Inhibition of metabolism according to the principle of feedback. Analogues of metabolites, in addition to direct inclusion in metabolism, can function as repressors. With a high content of purines and pyrimidines in the cell, their synthesis is inhibited, an excess of histidine inhibits the activity of the first of seven enzymes involved in the biosynthesis of this amino acid from ribose-5-phosphate and ATP, large doses of uridine inhibit the synthesis of orotic acid. This universal mechanism of autoregulation of metabolism is one of the potentially possible ways of correcting metabolism in genetic disorders of metabolism and is of particular relevance in the search for antimetabolites used in the field of chemotherapy.

1.3. Modern metabolic drugs

Metabolic drugs occupy a significant place in general clinical practice today. Most of them are low-toxic compounds, which allows treatment by varying doses in a wide range and usually providing simultaneous effects on different body systems (Galenko-Yaroshevsky et al., 2001; Chekman et al., 2007-2019).

Until now, there is no single classification of metabolic drugs. At the same time, it is advisable to divide the multitude of drugs used in experimental and clinical pharmacology into the following groups, although the division is conditional, the same drug may belong to different groups.

Drugs of metabolic type of action

Substrates of energy exchange

Macroergic compounds and their components: ATP, ATP-long, adenosine, inosine (riboxin), creatine phosphate (neoton), etc.

Metabolites of glycolysis and the pentose phosphate cycle: glyceralaldehyde-3-phosphate, fructose-1.6-diphosphate, hexose phosphate, phosphoenolpyruvate, etc. (experiment).

Substrates of the cycle of tricarboxylic acids

Succinic acid and its derivatives (limontar, reamberin, mexidol, Mexicor, yakton)

Malonic acid and its derivatives (stimol-citrulline malonate, potassium malonate, sodium malonate, citrulline malonate)

Alpha-ketoglutaric and fumaric acids (experiment).

Enzymes of energy exchange

Nicotinamide

Nicotinamide dinucleotide (experiment).

Components of the respiratory chain

Riboflavin

Nicotinamide

Cytochrome C

Ubiquinone (coenzymeQ).

Substrates and modulators of lipid metabolism

Substrates of lipid exchange: phospholipids (essential), lipin.

Modulators of lipid metabolism: carnitine and the drug containing it (cardonate), trimetazidine, mildronate.

Antioxidants: (thiotriazoline, quercetin, mexidol, emoxipin, ritmokor, corvitin, lipoflavone, etc.).

Means of correction of protein metabolism

Purine and pyrimidine bases and their derivatives (methyluracil, folic and orotic acids, potassium orotate, Magnerot, sodium nucleicate, inosine).

Amino acids and drugsthat contain them: asparkam (panangin), methionine, acetylcysteine, taurine (diacor), cratal, arginine, glycine, L-lysine-escinate.

Dipeptides and other amino acids and their derivatives: carnosine, dalargin, noopent, etc.

Modulators of NO-synthase: L-arginine, glutargin, korargin, citrarginine, etc.

GABA and its derivatives: (aminalon, picamilon, noofen, pantogam, fenotropil memoplant) and others.

Hormonal drugs.

Enzyme preparations, except for those mentioned above.

Vitamin preparations, except for those mentioned above.

Macroergic compounds and their derivatives do not lose their importance.

Adenyl nucleotides- high-energy compounds that act as carriers of phosphoryl groups of ATP, which is necessary for various reactions, including the synthesis of proteins and nucleic acids, is a source of energy during the contraction of muscle fibers, and also ensures the operation of transmembrane pumps. Only to ensure the pumping function of the heart, the myocardium generates about 36 kg of ATP. Although ATP was the first among the components of adenyl nucleotides to be used in clinical practice, the attitude of clinicians to it as a drug is quite controversial. After the initial positive opinion about the effectiveness of ATP, a few years later the opinion that ATP is ineffective due to the impossibility of its transmembrane transfer due to the large size of the cell molecule began to prevail. However,

ATP is involved in the processes of neuronal and neuromuscular impulse transmission, acting as a modulator of synaptic transmission. The mediating function of ATP has been discussed in detail in a number of fundamental reviews (Chekman et al., 2009).

Due to the effect on synaptic purinergic structures, ATP temporarily increases the tone of blood vessels of the small circle of blood circulation. ATP is quickly hydrolyzed with the formation of ADP, AMP, adenosine, which are quickly taken up by tissues and therefore determine the main mechanism of action. ATP can directly affect the formation of prostaglandins. Agonists of adenosine receptors and adenosine itself have a cardioprotective effect, directly affecting the sinus node. The negative myotropic and chronotropic effects of adenosine and the stimulation of glycogenolysis in the myocardium are the main factors that ensure the protection of the myocardium.

One of the important tasks of metabolitotropic therapy is to ensure the energy exchange of organs and tissues during ischemia and hypoxia. In cells, ATP is necessary to ensure many reactions as a carrier of phosphate groups. The drug participates in the synthesis of proteins and nucleic acids, serves as a source of energy during muscle contraction, including myocardial fibers, participates in the processes of neuronal and neuromuscular impulse transmission, acting as a modulator of synaptic transmission. There are also data on the stimulation of prostaglandin synthesis by adenosine with a subsequent vasodilating effect. Although there are data on the regulatory effects of ATP on various functions of the body, the possibility of penetration of the ATP molecule intracellularly is denied by researchers. The sodium salt of ATP, which is administered intramuscularly or intravenously, is mainly used.

Despite the fact that in conditions of ischemia, the synthesis of ATP decreases, and the direct introduction of ATP should lead to an increase in energy reserves in the cell and a further decrease in the manifestations of ischemia, the sodium salt of ATP does not have a significant effect, due to the impossibility of entering the cell. Therefore, there was a need to create a new drug that would significantly affect intracellular metabolic processes, in particular, energy potential. The creation of such a drug was based on taking into account the following biochemical features. ATP in the body is a biological complex-forming reagent that manifests its main metabolic and hemodynamic effects in a complex with magnesium. Most exchange reactions require not only the

participation of ATP as a metabolic substrate, but also magnesium as a cofactor. Magnesium has a decisive influence on the biological activity of ATP, preventing its destruction by inhibiting the processes of deamination and dephosphorylation of ATP by tissues. For the successful correction of disorders associated with ischemia and cell damage, the use of the ATP-magnesium complex is required (Chekman et al., 2009).

The use of ATP together with Mg has a multifaceted effect on the physiological and biochemical processes occurring in the cell. This complex in the post-ischemic period increases the content of intracellular ATP, reduces the concentration of lactic acid in tissues, improves electrolyte metabolism, normalizes membrane permeability, increases the level of calcium and magnesium in mitochondria, and reduces intracellular acidosis.

ATP-long is the first original domestic drug that is a coordinating compound. In terms of its chemical structure, it has no analogues. The drug was obtained by directed synthesis in such a way that its components: macroergic phosphate, magnesium ion, amino acid histidine and potassium ions are coordinated so that the molecule is easily incorporated into various links of metabolic processes and has an affinity for cell membrane receptors. In the course of preclinical and clinical studies, it was shown that the drug ATP-long has the following pharmacological effects:

–cardioprotection in conditions of ischemia;

– increasing the energy resources of myocardial cells;

– suppression of the intensity of oxidative stress;

– increasing the activity of ion transport systems, Na+, K+-ATP-ase and Ca2+-ATP-ase, increasing the calcium-binding potential of the membrane, normalizing the level of potassium and magnesium in the myocardium;

– improvement of indicators of central and peripheral hemodynamics, coronary blood circulation.

The use of ATP-long is indicated for the following diseases and syndromes:

– paroxysmal supraventricular tachycardia;

– other rhythm disorders (as part of complex therapy);

– ischemic heart disease, stable angina pectoris

– postinfarction and myocardial cardiosclerosis;

– vegetative-vascular dystonia of the cardiac type;

– myocardial dystrophy;

– chronic fatigue syndrome;

– hyperuricemia.

The use of the drug ATP-long for the correction of fetoplacental insufficiency in pregnant women (in a dose of 30-60 mg / day for 2-3 months) with extragenital pathology (dysfunction of the thyroid gland, neurocirculatory dystonia) made it possible to stabilize central hemodynamics and reduce the frequency of such complications as: hypoxia of the fetus during childbirth, anomalies of labor activity, late and premature childbirth; reduce the number of cesarean sections. Research is being conducted on the use of ATP-long in the complex therapy of newborns after perinatal hypoxia.

The desire of pharmacologists and clinicians to increase the efficiency of restoration of energy resources in the cell during ischemia and hypoxia led to the creation of another drug containing macroergic compounds – phosphocreatine (neoton). Phosphocreatine is a key substrate in the transport system of macroergs to the places of their utilization. A decrease in the concentration of phosphocreatine in the cell below a critical level coincides with the destruction of the membrane and the beginning of irreversible changes in the cell, phospholipolysis and oxidative stress are initiated.

Although cell membranes are considered impermeable to polar compounds such as phosphocreatine, there is experimental evidence of the possibility of its entry into the cell under certain physiological and pathological conditions. Creatine and phosphocreatine participate in the transfer of energy from mitochondria to the places of its utilization, increase the energy potential and the pool of adenyl nucleotides as a result of the activation of phosphoribosylpyrophosphatase (the key enzyme of nucleotide synthesis) in two ways: indirectly through an increase in the level of ATP and directly due to the elimination of the inhibitory effect on the level of ADP. The drug reduces the harmful effect of ischemia on the cell membrane. Under the influence of phosphocreatine, there is a change in the hormonal regulation of metabolism, which is based on the activation of the pituitary-adrenal system, stimulation of adaptive protein synthesis,

The mechanisms of biochemical effects of phosphocreatine are diverse and consist of:

1) inhibition of platelet aggregation by removing ADP during the extracellular creatine kinase reaction;

2) penetration of a certain amount of phosphocreatine into cells and its participation in the energy transport system by maintaining high local concentrations of ATP;

3) inhibiting the degradation of adenyl nucleotides at the level of the 5-nucleotidase reaction occurring in the sarcolemmal membrane of cardiomyocytes;

4) inhibiting the accumulation of lysophosphoglycerides in the ischemic myocardium and ensuring the preservation of the structure of the sarcolemma of myocardiocytes;

5) the transition of the cell membrane to a more ordered state, as a result of the electrostatic interaction be-

tween the drug molecule and phospholipids in the presence of calcium ions.

Given that charged phospholipids are located on both sides of the sarcolemma, exogenous and endogenous phosphocreatine may be equally important for its stability. Rapid depletion of cellular phosphocreatine during ischemia can be one of the factors of membrane destabilization and increased rate of its destruction. Exogenous phosphocreatine can stabilize the membrane after attaching to its outer surface without penetrating the cells.

In conditions of hypoxia, administration of phosphocreatine is accompanied by inhibition of oxidative stress reactions, reduction of organic damage to cell membranes. The drug is prescribed as part of the complex therapy of acute cerebral circulation disorders, encephalopathy.

Over the past 20 years, a new approach to finding drugs with a metabolic type of action has been approved. Practical medicine includes drugs of synthetic origin, which have heterocyclic compounds in their structure, which are most often found in body tissues. Currently, one of the most widely used metabolitotropic drugs is the imidazole derivative trimetazidine (preductal, triductan), which has a cytoprotective effect on the myocardium and brain and, according to the decision of the European Association of Cardiology, is recognized as one of the most effective. Cytoprotection with the introduction of trimetazidine is carried out due to the intensification of the supply of energy to the cell. This is achieved by partially inhibiting the oxidation of fatty acids as a result of inhibiting the activity of 3-ketoacylcoenzyme A-thiolase and switching myocardial metabolism to glucose oxidation. This prevents the development of intracellular acidosis and calcium overload, ensures maintenance of ATP production and preservation of contractile function. The drug improves the functioning of the myocardium, restores the operation of ion pumps. Membrane protection to some extent is due to an increase in phospholipids due to a change in the utilization of fatty acids, which ensures the resistance of the cell to damage during ischemia-reperfusion.

The protective effect of trimetazidine on the level of ATP and creatine phosphate in total hypoxia of the heart and brain was established. At concentrations close to therapeutic levels in blood plasma, trimetazidine accelerated the recovery of cell energy reserves during reperfusion. Trimetazidine preserved mitochondrial energy potential by restoring calcium-blocked ATP synthesis and preventing hypoxia-induced ATP hydrolysis. In addition, trimetazidine corrected ion imbalance, reduced intracellular acidosis caused by ischemia. In conditions of acidosis, trimetazidine inhibited the intracellular accumulation of Ca^{2+} and Na^{+}.

In in vitro studies, trimetazidine dose-dependently inhibited platelet aggregation induced by collagen, arachidonic acid, and to a lesser extent thromboxane A2 analog (calcium ionophore) and ADP. It was established that the effect of trimetazidine consists in inhibiting the cascade of transformations of arachidonic acid and thereby reducing the production of thromboxane A2. The mechanism of the antiplatelet effect of trimetazidine is similar to its antiradical effect, since free radicals cause membrane damage and, therefore, stimulate the cascade of transformations of arachidonic acid. In model experiments on isolated rat myometrium, the β2-sensitizing effect of trimetazidine was established, which is realized by three main factors:

1) due to an allosteric change in the conformational state of beta-adrenoceptors, as a result of which the affinity to the agonist increases;

2) inhibition of the activity of enzymes (beta-adrenoceptor kinase, protein kinase A and B-arrestin) involved in the phosphorylation of beta-adrenoceptors, due to which the receptors lose their affinity for the agonist;

3) by increasing the activity of phosphatase, which is involved in the dephosphorylation of beta-adrenergic receptors and, thereby, restoring their affinity to the agonist.

Thus, trimetazidine cytoprotection is:

1. Suppression of the activity of 3-ketoacyl coenzyme-A-thiolase;
2. Inhibition of fatty acid oxidation and enhancement of glucose oxidation in the myocardium with inhibition of mitochondrial thiolase;
3. Limitation of intracellular acidosis and oxidative damage to the cell during ischemia;
4. Antiplatelet effect;
5. Preventing the accumulation of calcium and sodium in cells;
6. Antioxidant and antiradical action;
7. Antihypoxic effect;
8. Inclusion of long-chain fatty acids in sarcolemma lipids;
9. Activation of phosphatidylinositol synthase, increased formation of phosphatidylinositol phosphate.

Mildronate also has well-expressed cytoprotective properties, although it cannot be considered a reference cytoprotector, because a significant place in its mechanism of action is occupied by a change in hemodynamic parameters. In conditions of ischemia, the supply of oxygen to the cells is limited and insufficient for the oxidation of fatty acids. As a result, underoxidized acylated forms of fatty acids (acetcarnitine and acylcoenzyme A) accumulate in mitochondria, which, on the one hand, block the transport of ATP into the cytosol, and on the

other, being detergents, destroy membranes. Therefore, by blocking the biosynthesis of the carnitine fatty acid carrier, mildronate maintains a sufficient level of ATP, prevents disruption of the process of aerobic glucose oxidation, and promotes the biosynthesis of the natural inhibitor of carnitine biosynthesis – gamma-butyrobetaine. The drug also activates hexokinase and pyruvate dehydrogenase enzymes, normalizes the tone of blood vessels, prevents the development of myocardial hypertrophy. The drug is safe and has very low toxicity (Shaforostova et al., 2022).

A number of studies confirmed the high clinical effectiveness of mildronate in disorders of cerebral circulation, hypoxic encephalopathy, including in children

Created at the Latvian University of Organic Synthesis, mildronate is a structural analogue of gamma-butyrobetaine, which disrupts the conversion of gamma-butyrobetaine into carnitine by inhibiting the activity of gamma-butyrobetaine hydroxylase. The basis of the action of the drug is a decrease in the concentration of carnitine. When the concentration of carnitine in the cytoplasm decreases, the rate of transport of fatty acids into the mitochondria also decreases, which in turn contributes to the restoration of the transport of already produced ATP into the cytosol. An increase in the concentration of fatty acids in the cytoplasm is a kind of signal to the cell that the oxidation of fatty acids is impossible for some reason. The body responds to such a signal by turning on glucose oxidation mechanisms. The results of the conducted research (Chekman et al., 2009-2022) indicate that mildronate is a representative of a group of pharmacological agents – inhibitors of the polyphosphoinositide system of cell signaling, with pronounced polytropic action, allowed us to assume that the direct metabolic effects of mildronate, in particular its effect on cell signaling systems, and part of the metabolic effects may be mediated by «signaling « by the action of the drug.

It has been established that mildronate activates both of the most important enzymes of the cycle of aerobic glucose oxidation:

• hexokinase, which involves not only glucose, but also other hexoses in the oxidation process;

• pyruvate dehydrogenase, which involves pyruvate formed from sugars in the Krebs cycle, thereby preventing the formation of lactate (acidosis).

It should be especially emphasized that under the influence of mildronate, not only the activity of these enzymes increases, but also their biosynthesis is induced, that is, the number of these most important enzymes also increases.

The increase in the concentration of NO explains the increase in the elasticity of erythrocytes under the effect of course administration of mildronate. Together, these effects determine the positive effect of mildronate on microcirculation and in the treatment of patients with blood circulation disorders in the brain.

Inhibition of GBB-hydroxylase by mildronate is reversed: mildronate does not block this process, but occupies the catalytic center of GBB-hydroxylase, thus preventing the conversion of GBB into carnitine II.

The biochemical mechanism of action of mildronate is due to:

1. Suppression of the transport of fatty acids, as a result of which:

• switching of ATP synthesis in mitochondria from the oxidation of fatty acids to the oxidation of carbohydrates;

• induction of biosynthesis of key enzymes of energy metabolism.

2. Activation of NO biosynthesis, which is expressed in the improvement of blood rheology and in the reduction of peripheral resistance.

Thus, mildronate in conditions of ischemia:

• reduces the flow of fatty acids into the cytosol and mitochondria; as a result, the concentration of strong detergents – acyl-CoA and acylcarnitine in cells decreases;

• inhibits p-oxidation – as a result, the need for cells in exogenous oxygen decreases;

• restores transport of ATP from places of biosynthesis (mitochondria) to places of consumption (cytosol);

• contributes to the biosynthesis of GBB and increases its concentration, normalizes the tone of blood vessels and, over time, restores the normal concentration of carnitine.

Mildronate:

• activates hexokinase (an enzyme involved in the oxidation of many sugars) and stimulates its formation in cardiomyocytes;

• stimulates pyruvate dehydrogenase;

• promotes glucose oxidation in conditions of oxygen deficiency, stimulating energy production without the formation of lactic acid.

Mildronate is used in the complex therapy of hypoxic-ischemic encephalopathy of the newborn – 10% solution 0.1-0.2 ml / kg / day IV or IV.

Arachidonic acid (AC)- the predecessor of the PG of the 2nd series and the LT of the 4th series. At the same time, omega-3 PUFA is a substrate for the synthesis of PG 3 and LT 5 series. Upon arrival eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) with food (the body does not synthesize these acids) they partially replace omega-6 PUFAs in the membranes of platelets, erythrocytes, neutrophils, monocytes, hepatocytes and other cells. Competition between arachidonic acid and

omega-3 PUFAs at the cyclooxygenase-lipoxygenase level is manifested by a modification of the PG and LT spectrum:

• production of prostaglandin metabolites decreases

• the level of thromboxane A2, a powerful vasoconstrictor and activator of platelet aggregation, decreases:

• formation of LTV4, an inducer of inflammation, chemotaxis and adhesion of leukocytes decreases:

• the plasma concentration of thromboxane A3, a weak vasoconstrictor and inducer of platelet aggregation, increases;

• the level of prostacyclin I2 (PGI2) increases, which in the absence of a decrease in prostacyclin E2 (PGE2) leads to an increase in the concentration of total prostacyclin. PGI2 and PGE2 are active vasodilators and inhibit platelet aggregation;

• the concentration of LTV5, a weak anti-inflammatory agent and chemotaxis factor, increases.

The mechanisms of the action of omega-3 PUFAs on other links of the hemostasis system (in particular, a reduction in the content of fibrinogen, activation of the fibrinolysis system) have not been fully elucidated.

The hypolipidemic effect of fish oil consists in inhibiting the synthesis of very low and low density lipoproteins, improving their clearance and increasing bile excretion.

AK is an essential acid. Of course, it is necessary for the body. Its metabolites perform important regulatory functions, and since in health conditions the most important thing is to maintain muscle tone, preserve the integrity of blood vessels, prevent bleeding, then among the metabolites of AK the substances with broncho- and vasoconstrictor properties prevail (PGF2a, LT 4th series), inducers of aggregation of formed blood elements (Tx A2). And products with anti-inflammatory properties (PGI3, PGE) have relatively few metabolites in total. In healthy conditions, when excessive vasoconstriction and bronchoconstriction are not needed, there is no need for an excess of vasodilators and bronchodilators. But in the conditions of the disease, this non-specific compensatory and adaptive reaction is transformed into a pathological one.

Thus, when the body is sick, EPA metabolites are more beneficial, as substances with antispasmodic and platelet aggregation inhibiting properties prevail among them.

Liposomeswere first discovered in 1964 in the form of an aqueous dispersion of phospholipids that form closed structures consisting of a lipid bilayer and an aqueous phase in its middle. In the 38 years that have passed since their discovery, liposomes have gained wide popularity and aroused great interest from specialists in the field of biochemistry, biophysics, cell biology and experimental pharmacology as models of biological membranes, reaction, vector systems for the transport of various macromolecules in vivo, as well as for the introduction of foreign molecules and viruses into the cell.

Research on the use of liposomes as carriers of medicinal substances was started in the 70s. Liposomal structures have been shown to have significant advantages over other possible carriers. The structural similarity with natural biomembranes and the proximity of physicochemical characteristics made it possible to study with the help of liposomes the permeability of phospholipid bilayers to water, ions, carbohydrates, to reconstruct some intermembrane channels, enzyme systems and receptors, to reveal the peculiarities of the initiation of oxidative stress by blood leukocytes, to clarify the mechanisms of immune reactions.

Liposomes are able to significantly reduce the fluidity and permeability of the cell membrane, while significantly modifying membrane structures, restoring the functional activity of cells, in general. They replace oxidized forms of phospholipids and cell membrane defects with liposomal lipids. Accumulating mainly on cells with a depolarized membrane due to their small size and significant total surface, liposomes absorb substances with a small and medium molecular weight. Phospholipid vesicles can be introduced into the body of humans and animals by any method known in medicine. The most studied intravenous method of administration. The largest amount of liposomes enters the liver, kidneys and spleen. After intravenous administration, 50-80% of liposomes are absorbed within 40 minutes by cells of the phagocytic mononuclear system, primarily Kupffer cells and hepatocytes. Even in the case of intratracheal administration of phosphatidylcholine (FHL), the largest number of markers was detected in the liver (up to 5% of the administered dose), kidneys (up to 1.6%), spleen (up to 1.2%). Thus, the inhalation of FHL determines the occurrence of not only a local, but also a general pharmacological effect.

The prospect of using phosphatidylcholine liposomes as an independent therapeutic agent could not fail to attract the attention of researchers. Considerable interest in FHL is due, first of all, to the fact that lecithin has antioxidant and reparative properties, affects lipid metabolism, the surfactant system, and the phospholipid composition of the lung parenchyma. Secondly, the liposomal form of FHL, which is a model of biomembranes, involves the active influence of phospholipids on cell membranes and their receptors, on the reactions of oxidant and nitrosating stress, the activation of which plays a significant role in the pathogenesis of many diseases.

The use of liposomes in such a modern field of medicine as gene therapy is also promising. Liposomes can be a unique container for transferring genetic material to various organs and tissues of the body.

In the literature, there are data that testify to the anti-inflammatory effects of FHL due to the ability to reduce the severity of swelling and alteration of soft tissues, suppress the growth of conditionally pathogenic microflora.

Experimental work, which was performed on various models of hypoxia, showed that inhalation and intravenous administration of FHL helped to increase the body's resistance to all types of hypoxic effects. The antihypoxic effect of FHL is associated with the improvement of oxygen supply to tissues, reduction of the degree of tissue hypoxia and lactic acidosis, suppression of oxidative stress reactions, and reduction of release of underoxidized metabolic products into the blood. The antioxidant effect of FHL is ensured by maintaining a high antioxidant status of both the enzymatic and non-enzymatic links of the antioxidant system (AOS). The introduction of FHL helps restore the activity of enzymes (superoxide dismutase and catalase) in brain, liver and heart tissues and increases the level of cytochromes B5 and P450.

In case of stress, FHL prevents a significant decrease in the content of adenosine triphosphoric acid and creatine phosphate, which ensures the preservation of the total energy potential of hepatocytes and cardiomyocytes. The antiarrhythmogenic and cardioprotective effect of FHL was also noted, especially in the case of various shock conditions. During the study of central hemodynamics in patients with chronic obstructive bronchitis who received FHL, an increase in stroke volume and cardiac index was found.

The use of FHL in the complex treatment of pregnant women with hypertensive disorders has an antioxidant effect – it reduces the amount of products of oxidative protein modification, increases the content of a-tocopherol and the activity of superoxide dismutase. The inclusion of FHL in the complex of medical measures for pregnant women with iron-deficiency anemia makes it possible to reduce the frequency of blood transfusions, contributes to a more complete recovery of hematological indicators, and also significantly reduces the frequency of obstetric pathology during childbirth, in the postpartum period and in newborns.

Due to its unique properties and non-toxicity, FHL is recommended for use in pediatric practice in case of fetal hypoxia, pneumonia, lung atelectasis, respiratory dysregulation associated with perinatal hypoxia during childbirth; with bronchitis, bronchial asthma and other diseases that are manifested by a violation of the transport of oxygen into the blood and from the blood into the tissues. There are reliable data on the high efficiency of exogenous phospholipids in perinatal fetal hypoxia (Shabalov & Tsvelev, 2004).

It was established that the appointment of essentiale in the form of intravenous infusions (10 ml in 200-300 ml of 5% glucose solution) with simultaneous oral administration of the drug (7 capsules per day) and subsequent oral administration until the delivery date in the same dosage leads to an improvement in uterine -placental blood flow, diffusion properties of the placenta, normalization of metabolic processes in the fetus. Possessing antioxidant activity, the drug helps reduce the intensity of lipoperoxidation processes, restore the structure and normalize the functions of biological membranes. The appointment of the drug leads to a significant improvement in pregnancy outcomes for the fetus. (Shabalov & Tsvelev, 2004).

It is known that magnesium ions have an antagonistic effect on calcium ions, which is accompanied by a cytoprotective effect. In addition, magnesium is a blocker of NDMA-dependent calcium channels, through which its neuroprotective effect is mediated. It is thanks to these properties that magnesium is included in the treatment regimens for acute cerebral circulation disorders as a primary neuroprotector. Magnesium sulfate is used for this. But we have established that its combination with amino acids (glycine, GABA, tryptophan), which themselves have a neuroprotective effect, shows a more pronounced effect (Belenichev et al., 2009-2019).

Magnesium ions participate in no less than 300 metabolic reactions, and thus have a positive effect both directly and indirectly. In addition, patients with damage to the central nervous system or the cardiovascular system have its deficiency, which requires correction. Magnesium deficiency in the body is a phenomenon characteristic of the population of the entire modern world. Magnesium is the second most abundant cation after potassium in the intracellular space in the body.

Magnesium is one of the most important minerals used in oral chelation therapy. It stimulates the exchange and absorption of other mineral substances, primarily calcium, phosphorus, potassium, sodium. It also accelerates the process of assimilation of vitamins of group B, vitamin C and vitamin E. Magnesium is necessary for the normal functioning of myocardial cells. When using various forms of magnesium salts, stimulation of energy metabolism and acceleration of ATP synthesis is observed. Magnesium takes an active part in the transmission of nerve impulses. Magnesium ions are natural antagonists of calcium ions.

When using magnesium in the form of a complex with ATP – ATP-Mg, cardiac output increases with si-

multaneous intensification of oxygen utilization. Chronic fatigue syndrome is a necessary companion of stress, which is a consequence of magnesium deficiency in the body. In the body, magnesium has a pronounced ionic asymmetry: its concentration in cells is 3-15 times higher than in plasma.

Magnesium deficiency is not only always accompanied by a decrease in the level of potassium and calcium, but also causes hypokalemia and hypocalcemia, as well as worsens their manifestations. This element is quite often found in food products: in fresh green vegetables, wheat germ, soybeans, figs, corn, apples, seeds and nuts, especially in almond kernels. But its daily dose, necessary for the body, often does not come with food, and it makes sense to develop drugs that contain metabolically active magnesium. Based on the fact that 1 kg of body weight per day requires 5 mg of magnesium, the need for magnesium for men and women is calculated. This value changes with age, as well as depending on the loss of this element. Persons with heavy physical exertion, including athletes, should increase the daily dose by 10-15 mg per day (Table 1).

Table 1

Norms of physiological need for magnesium, mg per day

Age, physiological state	The norm of physiological need
0-3 months	55.0
4-6miss	60.0
7-12 months	70.0
1-3 years	150.0
4-6 years old	200.0
6 years old (schoolchildren)	250.0
7-10 years old	250.0
11-13 years old	300.0
14-17 years old	300.0
Older than 17 years	400.0
Pregnant and lactating women	450.0

Magnesium is a universal regulator of biochemical and physiological processes in the body: it participates in energy, plastic and electrolyte exchange (Fig. 1).

Magnesium functions with high efficiency as a cofactor of more than 300 known enzymatic reactions, includ-

Energy exchange ↔ Plastic exchange ↔ Electrolyte exchange

↓ ↓ ↓

Magnesium lowers the level of sodium and calcium ions in the cell, and increases the level of potassium ions in the cell

↓ ↓ ↓

Polarization of the cell membrane

↓ ↓ ↓

Increases the energy potential of the cell	***Strengthens metabolic processes***	***Antagonism with calcium***
Formation of complexes with ATP molecules and activation more 300 enzymes	Participation in protein synthesis	Ensuring muscle fiber relaxation
Prevention of uncoupling of oxidation with phosphorylation	Participation in the synthesis of fatty acids and lipids	Inhibition of release acetylcholine from presynaptic end
Regulation of glycolysis	Participation in the synthesis and decay of nucleic acids	Norepinephrine binding in granules (inactivation and reservation)

Fig. 1. The role of magnesium in the regulation of metabolic processes

ed in a wide range of metabolic activity, thus exerting a positive effect directly and indirectly. Due to its ability to come into contact with organic substances, magnesium participates in the metabolism of enzymes, such as creatinine phosphokinase, adenylate cyclase, Ca-ATP-ase, enzymes of protein synthesis, glycolysis, which are involved in the transport of ions. In patients with damage to the central nervous system and other vital systems, when magnesium deficiency is observed and correction is necessary, administration of magnesium preparations plays a substitute role.

Magnesium provides hydrolysis of ATP, reducing compounds of oxidation and phosphorylation (increases the efficiency of reactions in which ATP is synthesized). The element regulates glycolysis, reduces the accumulation of lactate, participates in the oxidation of fatty acids and the activation of amino acids (Chekman et al., 2007-2019). Magnesium is necessary for the biosynthesis of proteins, transmission of genetic information through the production of DNA and RNA nucleotides, participates in the synthesis of cyclic AMP. It is believed that neuronal memory, which is implemented through potential-dependent N-methyl-D-aspartate sensitive receptors, is regulated by magnesium. The antidegenerative effect of magnesium valproate on the culture of cerebral neurons was shown. The influence of magnesium is connected simultaneously with the content of lipoproteins and lipid peroxidation. Magnesium normalizes the activity of the nervous system, participates as a cofactor in many enzymatic reactions, is an anti-stress macroelement, reduces the excitability of neurons and the transmission of nerve impulses, participates in many metabolic processes, regulates phosphorus, carbohydrate and protein exchanges, stimulates the breakdown of nucleic acids. Magnesium helps the body adapt to the cold, serves as a structural component of bones and tooth enamel, participates in muscle relaxation of blood vessels and muscles, stimulates intestinal peristalsis and increases bile secretion. Magnesium preparations normalize arterial and intracranial pressure, prevent convulsive contraction of muscles, relieve spasms of blood vessels, chronic fatigue syndrome, help maintain acid-alkaline balance, lower blood cholesterol, have vasodilator and antispasmodic effects.

Magnesium is involved in the synthesis of brain neuropeptides (Chekman et al., 2016). It is part of 13 metalloproteins, a number of enzymes, including glutathione synthetase, which plays a significant role in the biochemical processes of the cortex, carries out the transition of glutamate into glutamine, implements the activity of NMDA receptors, and inhibits the processes of disruption in the cortex. Magnesium is a blocker of NMDA receptors, which mediates its neuroprotective effect and explains its purpose for the treatment of acute cerebrovascular disorders. For this, magnesium sulfate is used, and magnesium chloride is also used abroad, now its compounds with amino acids, vitamins and other biologically active substances are more often recommended. In combination with organic compounds, which themselves have a cytoprotective effect, magnesium has a more pronounced effect. With ischemic brain damage, as a result of a decrease in cerebral blood circulation, there is a violation of the function of the respiratory chain of mitochondria and energy metabolism, glutamate «excitotoxicity», a violation of the ionic homeostasis of the cell with an increase in the intracellular content of calcium ions, an increase in the synthesis of NO, the development of oxidative stress, the expression of early response genes, anoxic depolarization membranes and cell death (Belenichev et al., 2009-2019). Therefore, the search for methods of pharmacological correction of these disorders, as well as drugs that reduce the degree of neurodegeneration in brain ischemia, is an urgent task of modern pharmacology. At this time, there is an active search for new cerebroprotectors among substances that affect the glutamate and GABA-ergic systems, calcium and nitric oxide antagonists, antioxidants, neuropeptides, inhibitors of the expression of pro-inflammatory cytokines. Magnesium preparations are widely used in medicine. In medicine, a whole list of magnesium preparations is used, the single and daily doses of which significantly exceed the daily needs of the body.

So, for example, magnesium sulfate is most often used. It is produced in the form of a powder and a 25% solution in ampoules of 5, 10 and 20 ml. The ampoule drug is administered during hypertensive crises intramuscularly or intravenously in 10-20 ml in the form of a 25% solution of magnesium sulfate. This equates to 71 mg/kg for an average person weighing 70 kg. The same doses are used for analgesia during childbirth and for convulsions. In view of the above, it is clear that magnesium preparations are used in medicine in very significant doses.

Magnesium creates complexes with other metabolic substances that increase its absorption, inclusion in metabolic cycles, increased affinity to cell membranes, have a membranotropic effect, influence on energy exchange. It makes sense to use such drugs to improve the level of human health and to prevent diseases for a long time.

Magne-B6 – tablets containing magnesium lactate dihydrate 470 mg; pyridoxine hydrochloride 5 mg. District d/intr. application, amp: magnesium lactate dihydrate 186 mg; magnesium pidolate 936 mg; pyridoxine hydrochloride 10 mg.

Pyridoxine, which is a cofactor of the enzyme, is involved in many metabolic processes. Magnesium deficiency can be primary – due to congenital anomalies of magnesium metabolism or secondary – due to insufficient intake with food. The combination of vitamin B6 and magnesium is appropriate for the following reasons: vitamin B6 and magnesium complement each other's pharmacological effects; vitamin B6 increases the concentration of magnesium in blood plasma and erythrocytes and reduces magnesium excretion with urine; magnesium activates the process of biotransformation of pyridoxine hydrochloride into its active metabolite pyridoxal-5-phosphate in the liver. The combined use of vitamin B6 and magnesium compensates for the deficiency of these substances that occurs with poor nutrition, malabsorption syndrome, excess excretion and ensures optimal intake of magnesium.

Magnesium and vitamin B6 have a synergistic effect on the nervous system (Davtian et al., 2022). After all, vitamin B6 acts as a coenzyme at the final stage of dopamine biosynthesis. Therefore, when vitamin absorption is disturbed, dysfunction of the hypothalamic-pituitary system, changes in mood and behavior are possible. Estrogen-induced deficiency of vitamin B6 leads to a decrease in the synthesis of serotonin and tryptophan. Cerebral disorders are characterized by headache, dizziness, stress, depression, memory impairment. Like other magnesium preparations, Magne-B6 can affect the central nervous system, it is also a nootropic, antihypoxic drug, especially against the background of magnesium deficiency, and thereby increase mental performance.

Therefore, Magne-B6 proved to be effective not only in the regulation of vascular tone in hypertension, cerebral stroke, but also in the treatment of attention deficit hyperactivity disorder and autonomic dysfunction syndrome. The use of Magne-B6 in adolescents with early forms of cerebrovascular pathology both in monotherapy and as part of combined therapy with cavinton and bilobi significantly normalizes the level of magnesium in blood serum and is effective in vascular pathology with hyperconstrictor and hypoconstrictor variants of the vascular response.

The use of Magne-B6 in the hyperconstrictor variant of vascular tone disorders can potentiate the effect of cavinton. At the same time, the normotensive effect of therapy is manifested (symptoms of dizziness, headache are reduced). The combination of Magne-B6 with bilobiul potentiates the antiasthenic effect, reduces nervous excitability, and paresthesias.

Conducted experimental studies confirm that the level of magnesium controls the occurrence of ischemic and stress injuries, corrects mineral exchange in the cortex. Later, it was noted that the drug Magne-B6 participates in the formation of microelement homeostasis in ischemia of brain tissue. With magnesium deficiency, convulsive twitching of the muscles of the legs, face, neck, and back occur. The female body is very sensitive to fluctuations in the level of magnesium, therefore magnesium deficiency is associated with a wide range of complications of pregnancy, childbirth, as well as fetal pathology: at this time, Magne-B6 is prescribed for miscarriage. With hormonal dysfunction, the activity of the heart is disturbed. An important purpose of Magne-B6 is for the prevention of pregnancy termination, in case of in vitro fertilization. Therefore, the use of the drug should be prescribed at the beginning of hormonal therapy.

At this time, there are a number of drugs for the treatment of hypertensive disorders in pregnant women, but they have a wide range of side effects due to sufficient toxicity. Therefore, the spectrum of pregnancy complications is interdependent with such phenomena as the development of hypertensive disorders in pregnant women, fetal growth disorders.

One of the most serious complications of pregnancy is hypertensive disorders in pregnant women, which occupies a prominent place in maternal and perinatal mortality (Davtian et al., 2022). A leading role in the pathogenesis of hypertensive disorders in pregnant women is played by electrolyte imbalance, vascular disorders, angiospasm, impaired exchange and permeability of the vascular wall, changes in the rheological properties of blood (the ratio between the level of prostacyclin and thromboxane A2), an increase in the content of Willebrand factor, endothelin plasminogen activator, and endothelial cells.

The positive effect of Magne-B6 is manifested by a protective effect on the central and peripheral nervous system. The drug suppresses the processes of disturbance in the cortex of the large hemispheres, hypothalamic area, vascular-motor and respiratory centers, suppresses neuromuscular excitability. In hypertensive disorders of pregnant women, magnesium preparations also have sedative, hypotensive, anticonvulsant, dehydrating, and diuretic effects. The drug improves blood supply to vital organs (brain, eye, heart, kidney, liver, placenta). At the same time, the positive effect of magnesium on the immune status is also noted.

A decrease in intravascular aggregation correlates with a decrease in mean arterial pressure. The use of Magne-B6 3 times a day for two weeks in the I, II, III trimesters of pregnancy reduces not only the frequency of placental insufficiency, but also hypoxia of the fetus during childbirth and during cesarean section. An important

fact is the ability of Magne-B6 in hypertensive disorders in pregnant women to eliminate arteriolospasm, change blood circulation in the uterus and kidneys, and potentiate the effect of antihypertensive drugs.

The use of Magne-B6 during pregestation not only improves fetoplacental blood circulation, but also reduces the percentage of hypotrophic children born, improves the psycho-emotional status of the pregnant woman. Rarely, stomach pain, dyspepsia occur during drug treatment.

The use of Magne-B6 orally for four days by pregnant women with a threat of miscarriage revealed new aspects of its effect – a disaggregation effect on platelets and an immunomodulatory effect on lymphocytes. The effectiveness of the drug for the prevention of the threat of abortion is noted, especially in the I – II trimesters, when the drug load should be minimized.

Due to the fact that hypomagnesemia occurs in both pregnant and non-pregnant women with type 2 diabetes, they need the use of magnesium preparations, primarily Magne-B6. As a result, the need for tablet anticonvulsant drugs is reduced, glucose fluctuations are evened out.

In women who give birth for the first time and again with risk factors for placental insufficiency and the development of disorders in the mother-placenta-fetus system, the prophylactic use of Magne-B6 contributed to the prevention of hemodynamic decompensation, while improvement in blood circulation in the uterine and umbilical arteries was noted against the background of a decrease in the cerebral artery. Endocrine disorders did not occur when taking magnesium preparations (the level of chorionic gonadotropin in the blood serum probably increased, as well as estriol, placental lactogen with a simultaneous decrease in the level of cortisone and alpha-fetoprotein). In addition, after taking the drug, the frequency of premature rupture of the fetal membranes (from 24% to 10%), pathological preliminary period (from 22 to 8%), various anomalies of labor activity (from 18 to 6%), hypoxia of the fetus during childbirth (from 20 to 8%), moderate forms of infant asphyxia (from 22 to 8%). In turn, this helped reduce the rate of cesarean sections (from 26 to 10%) and perinatal losses (from 28 to 10%).

When prescribing the drug in the abortion clinic, it should be taken into account that Magne-B6 ensures the proper level of cellular metabolism, normalizes sleep, reduces pain in the lower abdomen, lower back, and controls the work of the intestines. In the process of prescribing the drug, it was discovered that Magne-B6 acts as a mild tranquilizer. The drug has a pronounced sedative effect, therefore unwanted effects were eliminated without complications in pregnant women.

Favorable combinations of Magne-B6 with other drugs, including thiotriazoline for prevention of pregnancy termination, have been described. At the same time, magnesium acted as a tocolytic and had fewer side effects compared to other drugs (Belenichev et al., 2014).

Magnerot Magnesium orotate. Magnesium – a natural physiological antagonist of calcium – takes part in the catabolism and anabolism of carbohydrates, proteins, fats and nucleic acids, in energy processes, in the conduct of nervous disorders, promotes myocardial contraction, suppresses neuromuscular transmission, has an antispasmodic effect, and increases resistance to stress. Orotic acid regulates metabolism, activates the processes of cell growth and regeneration, stimulates the cellular utilization of magnesium, and the manifestation of its metabolic effects. Orotic acid in a complex with magnesium has an additional therapeutic effect on the heart, gives a clear anabolic effect, improves energy processes in the myocardium.

Magnerot is used in complex therapy of all forms of coronary heart disease (angina, myocardial infarction), in arrhythmias, magnesium-dependent muscle spasms, arteritis. A positive effect is known for premature birth and threatened abortion. Magnerot can be prescribed during pregnancy and breastfeeding.

Magnerot can be used for a long time. It is possible to use Magnerot during pregnancy and during lactation (breastfeeding) according to the indicators, since the need for magnesium increases significantly during these periods. If its content is not balanced, it can lead to serious complications, including untimely pregnancy.

Magnesium sulfate – magnesium ions have a wide range of effects on the body. When taken orally, magnesium sulfate has a choleretic and laxative effect, when administered parenterally it has a depressing effect on the central nervous system (depending on the dose, a sedative, hypnotic or narcotic effect can be observed). The drug can improve cerebral blood circulation. Suppresses the release of mediators (mainly acetylcholine) in the central nervous system and peripheral synapses, slows down neuromuscular conduction, lowers blood pressure (especially against the background of hypertension), has an antispasmodic effect when urination is delayed. Reduces the excitability of the respiratory center; when administered in high doses can cause respiratory depression. Indications: as a sedative, antispasmodic, laxative, choleretic agent, in the early stages of hypertensive disease, in hypertensive crisis, eclampsia.

Magnesium citrate Magnesium citrate replenishes magnesium deficiency, normalizes metabolic processes, reduces the excitability of neurons.

Indication. Magnesium deficiency in the body, including with frequent intake of laxatives, alcohol, significant mental and physical stress.

Mexidol has an anti-ischemic and antioxidant effect, improves the functional state of the ischemic myocardium, stabilizes the membrane structures of the vascular wall, inhibits platelet aggregation, normalizes microcirculation disorders in the early stages of atherogenesis, has a hypocholesterolemic effect. The chemical name of the drug is 2-ethyl-6-methyl-3-oxypyridine succinate. Indications for use are acute coronary syndrome, atherosclerosis, chronic forms of CAD (Voronina et al., 2022).

The basis of the action of the drug is its antioxidant activity, the ability to inhibit free radical processes, the pronounced intensification of which is observed in ischemia of organs and tissues, especially in the period of reperfusion and in conditions of a critical decrease in blood flow. Mexidol increases the concentration of reduced glutathione, activates the endogenous antioxidant system of superoxide dismutase and ceruloplasmin, prevents a decrease in the activity of glutathione-dependent enzymes (glutathione peroxidase and glutathione reductase). The positive effect of mexidol on the modulation of the activity of membrane-binding enzymes, ion channels, receptor complexes, including benzodiazepine, GABA, acetylcholine, was revealed; improvement of synaptic transmission and plasticity of the brain. Mexidol contributes to the preservation of the structural and functional organization of membranes,

The positive effect of mexidol on the modulation of the activity of membrane-binding enzymes, ion channels, receptor complexes, including benzodiazepine, GABA, acetylcholine, was revealed; improvement of synaptic transmission and plasticity of the brain. Mexidol helps preserve the structural and functional organization of membranes, stimulates the activity of membrane enzymes – phosphodiesterase, adenylate cyclase, acetylcholinesterase. Mexidol inhibits the development of hyperenzymatemia of inducible NO synthase in the ischemic brain. In acute ischemia, the drug normalizes oxidation in the Krebs cycle and intensifies the energy-synthetic functions of mitochondria and increases the synthesis of ATP and creatine phosphate. The reason for the anti-ischemic effect of mexidol is the direct oxidation of succinate, which is part of its composition, which is evidenced by the increase in cellular respiration, which is accompanied by the recovery of flavinoproteins. Mexidol normalizes lipid metabolism, improving blood circulation in the brain. Mexidol is proposed for secondary neuroprotection in the treatment of HPMK, dyscirculatory encephalopathies, vegetative-vascular dystonia, and atherosclerotic disorders of the brain. For this purpose, mexidol is prescribed parenterally (jet or drip) in isotonic solution or Ringer-Lock solution. There are experimental and clinical studies evaluating the neuroprotective effect of mexidol in conditions of prenatal hypoxia. It was shown that Mexidol reduces the induction of apoptosis of CA1 neurons of the hippocampus in animals that have undergone perinatal hypoxia. It was shown that Mexidol reduces the induction of apoptosis of CA1 neurons of the hippocampus in animals subjected to perinatal hypoxia. Mexidol also preserved the functional activity of the mitochondria of the neurons of these animals. Mexidol, when administered as a course at a dose of 10-20 mg/kg/day, increased the effectiveness of traditional therapy in children with perinatal encephalopathy. Mexidol, when administered as a course at a dose of 10.0-12.0 mg/kg/day in children with rhythm disturbances against the background of perinatal encephalopathy of hypoxic-ischemic genesis, contributes to the restoration of the processes of autoregulation of cerebral hemodynamics in the form of normalization of vascular tone and cerebral blood flow rate and regression of neurological symptoms. The use of mexidol in the complex therapy of extrasystoles 1-P FC in young children has an antiarrhythmic effect in 56% of cases (including contributing to the complete elimination of arrhythmia in 17.2% of children), optimizing indicators of intracardiac hemodynamics and the dimensions of the heart cavities, as well as improving the function of the sinus node.

The addition of mexidol to cordarone treatment allows using 31.5% lower loading doses of the latter while maintaining the overall antiarrhythmic effect (76.3% with combined and 69% with monotherapy with antiarrhythmic drugs) and preventing the development of typical cardiac and extracardiac side effects (Voronina et al., 2022). An appropriate dynamic study of cerebral blood flow indicators for all young children with frequent extrasystole to assess the expressiveness of cerebral hemodynamic disorders and control the therapy. For newborns and young children with extrasystole I-II FK on the background of perinatal encephalopathy, it is advisable as part of neurometabolic therapy to prescribe mexidol at a dose of 10-12 mg/kg/day IV drip No. 10 with subsequent transition to oral administration of tablet form in the same dose up to 21-25 days. For young children with complex disturbances of rhythm (paired, group extrasystole) and conduction against the background of perinatal encephalopathy, it is advisable to add Mexidol in a dose of 10-12 mg/kg/day IV drip No. 10 with subsequent transition to oral administration in tablet form in the same dose to traditional antiarrhythmic therapy with cordarone,

The anti-ischemic effect was found in preparations of glucosamine, glycyrrhizic acid, etc. (Voronina et al., 2022). The drugs entered clinical practice on the basis of the fact that during ischemia in myocardial cells, the content of glycogen decreases, which these drugs restore. Subsequently, the compound was administered to diabetic patients with signs of myocardial ischemia. It was found that the drugs reduce mortality, and their effectiveness is due to an increase in the content of ATP inside the cell, a decrease in the osmolality of the overload, which is necessary for the work of Na+-K+-ATPase. Similar cardioprotection was found in carnosine, acetylcarnosine, bradykinin and bradycardic drugs, protein kinase C stimulators, nitric oxide and drugs that increase its level, openers of ATP-dependent potassium channels (nicorandil).

L-carnitine – belongs to the means with an anabolic effect, performs the function of the main cofactor of the metabolism of fatty acids in the heart, liver and skeletal muscles, plays the role of the main carrier of fatty acids in the mitochondria, where their beta-oxidation to acetyl-CoA occurs (Virmani & Cirulli, 2022). Acetyl-CoA is a substrate for the formation of ATP in the Krebs cycle. Carnitine promotes the release of metabolites and toxic substances from the cytoplasm, improves metabolic processes, increases work capacity, appetite, accelerates growth, causes an increase in body weight, reduces the functional activity of the thyroid gland, contributes to the normalization of the basic metabolism in hyperthyroidism. L-carnitine also reduces the symptoms of physical and mental overexertion, exhibits neuro-, hepato- and cardioprotective effects, reduces cholesterol in the body, slows down the formation of vascular atherosclerotic plaques, helps reduce myocardial ischemia and limit the post-infarction zone, stimulates cellular immunity, eliminates functional disorders of the nervous system. systems in patients with chronic alcoholism and other neurological diseases. Carnitine is successfully used in complex therapy of newborns, (Virmani & Cirulli, 2022). Newborns (experienced perinatal hypoxia with symptoms of hypoxic-ischemic (or hypoxic-hemorrhagic for premature babies) damage to the central nervous system by the type of cerebral ischemia (CI) and intraventricular hemorrhages of the I-II stage. Premature babies, as well as babies with posthypoxic cardiovascular disorders of the perinatal period of the main group received in addition to the standard measures for recovery and treatment, additional measures (optimal feeding, respiratory support, correction of electrolytes, infusion, antibacterial and diuretic therapy according to indications) 10 intravenous infusions of the drug L-carnitine with the transition to taking the drug per os at a dose of 50 mg/ kg/day in 2 doses up to 1 month. The drug, diluted in 20 ml of 5% glucose solution, administered intravenously at a rate of 20 drops per minute to the first subgroup (n = 23) at a dose of 80-100 mg/kg/day, the second (n = 20) – 50 mg/kg/day. The introduction of the injectable form of the drug L-carnitine into the treatment plan of full-term and premature children contributes to better body weight gain, faster regression of neurological changes, improvement of respiratory functions, formation of swallowing and sucking reflexes in premature children. The additional administration of L-carnitine intravenously is more effective in comparison with the use of only the standard treatment scheme, it contributed to the improvement of the clinical status and optimization of the postnatal activity of the cardiovascular system. We noted an effective reduction of signs of electrical instability and myocardial ischemia, recovery of heart rate and normalization of systolic and diastolic heart function, the size of heart cavities, reducing the diameter and hemodynamic significance of functioning fetal communications, restoring the circadian organization of the heart rhythm, as well as reducing the duration of rhythm pauses and the presence of arrhythmias. The fastest and most complete regression of the manifestations of posthypoxic cardiomyopathy was observed when the drug was administered for 10 days at a dose of up to 100 mg/kg/day and continued for up to 1 month. Intravenous infusions of the drug L-carnitine were tolerated by newborns satisfactorily and were not accompanied by clinically significant side effects. The fastest and most complete regression of the manifestations of posthypoxic cardiomyopathy was observed when the drug was administered for 10 days at a dose of up to 100 mg/kg/day and continued for up to 1 month. Intravenous infusions of the drug L-carnitine were tolerated by newborns satisfactorily and were not accompanied by clinically significant side effects. The fastest and most complete regression of the manifestations of posthypoxic cardiomyopathy was observed when the drug was administered for 10 days at a dose of up to 100 mg/kg/day and continued for up to 1 month. Intravenous infusions of the drug L-carnitine were tolerated by newborns satisfactorily and were not accompanied by clinically significant side effects.

Lysine – an irreplaceable amino acid, participates in all processes of assimilation and growth, promotes ossification and growth of bone tissue, stimulates cell mitosis, supports female sexual function. Normalizes microcirculation and has capillary protective effect. The coenzyme of vitamin B12 (cobalamid) has anabolic activity, activates the metabolism of carbohydrates, proteins and lipids, participates in the synthesis of methyl groups, in the

formation of choline, methionine, nucleic acids, creatine, stimulates bone marrow function, which is necessary for normal erythropoiesis. Cobalamid contributes to the normalization of impaired functions of the liver and nervous system, activates the blood coagulation system, and in high doses causes an increase in the activity of thromboplastin and prothrombin. Vitamin B1 coenzyme (cocarboxylase) has a regulatory effect on metabolic processes in the body. This drug plays a particularly important role in carbohydrate and fat metabolism, reduces the level of lactic and pyruvic acid in the body, improves glucose assimilation, nervous tissue trophicity, contributes to the normalization of the function of the cardiovascular system in case of heart rhythm disorders, angina pectoris. The coenzyme of vitamin B6 (pyridoxal-5-phosphate) plays an important role in metabolism, which is necessary for the normal functioning of the central and peripheral nervous system. The drug, which is a coenzyme of a large number of enzymes that act on the exchange of amino acids, contributes to the normalization of lipid metabolism, increases the amount of glycogen in the liver, improves its detoxification properties, catabolizes neuromuscular processes, which are especially important in childhood when mental and physical development is delayed, with chronic fatigue and asthenia. As the main enzymes, that ensure the metabolism of L-lysine, lysine-ketoglutarate reductase, saccharopine dehydrogenase and saccharopine oxyreductase are defined. Children with hereditary deficiency of these enzymes develop a syndrome of familial hyperlysinemia, which is manifested by a delay in the development of speech, hyperactive behavior and some neurological disorders. Pipecolic acid is a cyclic imino acid. As a metabolite of L-lysine, it was discovered in plants, and then in human physiological fluids. The specified Zellweger hyperpipecolatemia syndrome is a genetic disorder characterized by an increased level of pipecolic acid in the blood plasma due to a decrease in the activity of oxidase, which metabolizes the acid in tissues. Interesting data on the transport of L-pipecolic acid through the blood-brain barrier and its selective absorption by various brain structures. The highest absorption indices were established for the cerebral cortex, brainstem and cerebellum. The study of the absorption kinetics of L-pipecolic acid showed a two-component mechanism – with low and high absorption, which allowed us to make an assumption about the possible role in the regulation of neuronal function of this metabolite of L-lysine. In some studies, pipecolic acid is considered a neurotransmitter or neuromodulator and plays a role in central GABA inhibitory systems. A second metabolite of L-lysine that has also been hypothesized to have a neurotransmitter function is L-alpha-aminoadipate. In a study on slices of the cerebral cortex of rats, it was shown that the accumulation of this metabolite in slices is a stereospecific and Na-dependent process, and the release is stimulated by a high concentration of K+ ions in the presence of Ca2+ ions. It is also important to note the activity of L-alpha-aminoadipate as a weak competitive inhibitor of the absorption of L-glutamate and L-aspartate by cells. In recent years, special attention of both experimenters and clinicians has been attracted by the essential amino acid L-lysine as a promising metabolitotropic neuroprotector. It is known that the basis of the mechanism of action of L-lysine is its ability to transform in the body into pipecolic acid, which enhances the affinity of the GABA-benzodiazepine-receptor complex, and also has the properties of a partial antagonist of serotonin receptors. This is expressed in anticonvulsant, neurotransmitter and neuromodulating effects. There are a number of studies devoted to the study of neurotropic, immunotropic, pain-relieving properties of L-lysine (Fig. 2).

The most important property of lysine is its ability to form L-carnitine together with vitamin C. L-Lysine participates in the formation of collagen – the protein of connective tissues, so it is used in the recovery period. L-Lysine improves the assimilation of calcium from the blood and its transport into the bone tissue, in connection with which it can be an integral part of the program of treatment and prevention of osteoporosis. Taking L-Lysine and L-Arginine together strengthens the body's immune response, in this case L-Lysine increases the effectiveness of L-Arginine. The barrier role of the vascular endothelium as an active organ determines its main role in the human body: maintaining homeostasis by regulating the equilibrium state of opposite processes – vascular tone (vasodilation / vasoconstriction), anatomical structure of vessels (synthesis / inhibition of proliferation factors), hemostasis (synthesis and inhibition of fibrinolysis and platelet aggregation factors), local inflammation (production of pro- and anti-inflammatory factors). With prolonged exposure to factors such as ischemia, there is a change in the endothelial response with a tendency to dominance and chronic hyperactivation of vasoconstriction and hemocoagulation, growth and proliferation factors, which ultimately leads to the development of endothelial dysfunction (Belenichev et al., 2016).

Of the antioxidants of plant origin, quercetin should be noted, which is an aglycon of the flavonoid glycoside rutin (Chekman et al., 2007-2019). This bioflavonoid, available in granules, tablets and solution for injection, is able to prevent or eliminate the manifestations of oxidative stress. The drug exhibits antioxidant, antiradical, membrane-stabilizing properties due to the predominant

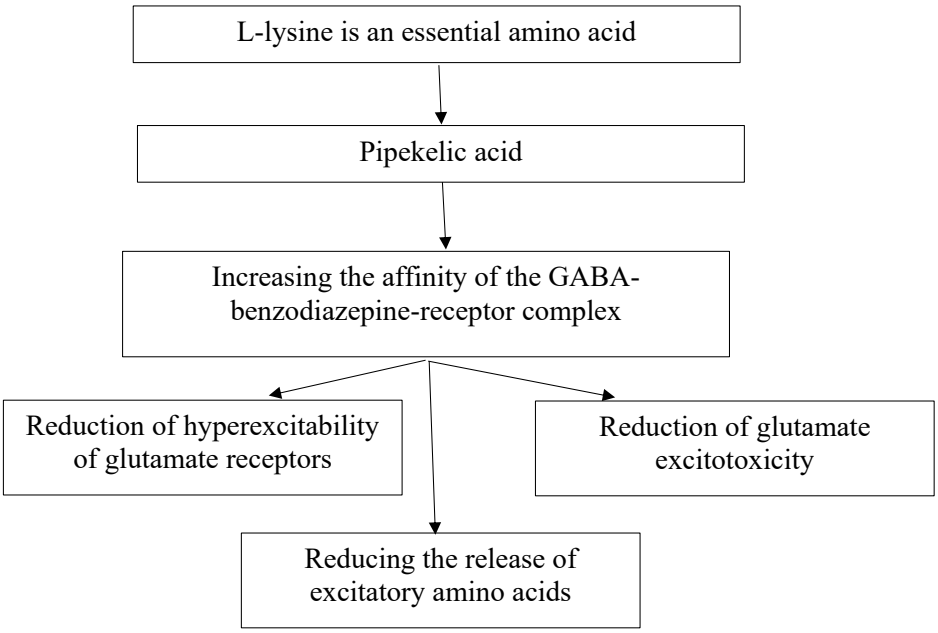

Fig. 2. The mechanism of action of the essential amino acid L-lysine

inhibition of the activity of lipoxygenases, as well as, to a lesser extent, phospholipases and cyclooxygenases. Quercetin prevents an increase in the level of potassium inside the cell, has a vasoprotective effect associated with the ability to release nitric oxide and inhibit protein kinase. Inhibition of protein kinases by quercetin is a very significant factor in the regulation of cell division and proliferation. Its participation in these vital processes of the cell, which depend on its development, course and/or the outcome of many pathological disorders, indicates the manifestation of multiple pharmacological properties. Features of the chemical structure of the quercetin molecule determine its ability to inhibit enzymes responsible for various oxidative reactions and processes. Such enzymes, in particular, are lipoxygenases and cyclooxygenases, which undergo biotransformation of arachidonic acid into such biologically active substances as leukotrienes and prostaglandins. Inhibition by quercetin of lipoxygenases of different subtypes (LO-5, LO-12 and LO-15) involved in the oxidation of arachidonic acid can be used to correct many pathological processes. Quercetin can act as a scavenger of superoxide radical, singlet oxygen and participate in the processes of inhibiting the formation of lipid hydroperoxide radicals. Quercetin, neutralizing aggressive oxygen-containing and nitrosyl radicals, interrupting the chain of free radical reactions (Di Petrillo et al., 2021). Administration of quercetin has been shown to reduce cognitive deficits in preterm rats with perinatal cerebral ischemia/hypoxia induced by traumatic brain injury by increasing the number of oligodendrocyte progenitor cells (OPCs) in the subventricular zone. Quercetin enhances the phosphorylation of the transcription factor CREB (cyclic-AMP Response Element Binding Protein) and increases the level of brain-derived neurotrophic factor (BDNF), which may be the mechanism underlying the increase in neuronal proliferation and synaptogenesis.

Taurine reduces the manifestations of intoxication by cardiac glycosides, and also potentiates the normalizing effect of cardiac glycosides on energy reserves. The attention of researchers is attracted to the product of cysteine denaturation – taurine, which was isolated in the 19th century from ox bile as a product of cysteine degradation. The chemical structure of taurine is 2-aminoethanol sulfonic acid (Chekman et al., 2009). According to modern classifications, the drug taurine belongs to metabolic drugs. These compounds were initially thought to be metabolically inert. Taurine is mainly found in excitable tissues. The highest content of cysteine is observed in organs where intensive metabolism takes place, therefore taurine is considered one of the most universal modifiers of the metabolism of nervous tissue, myocardium, liver, and the lens of the eye. Taurine content in tissues ranges from 2 to 30 μmol/kg, and in retinal cells reaches 50 mmol/kg (epithelium and photoreceptors) (Kolesnik et al., 2012-2013). Experimental and clinical studies have established that in various pathological conditions (starvation, hypoxia, diseases of the cardiovascular and hepatobiliary systems, radiation sickness, cataracts) there is a decrease in the content of taurine in the blood, brain tissue, liver tissue, and the lens of the eye. This became the basis for further

research into clinical and pharmacological properties of taurine, in particular, pharmacokinetics, pharmacodynamics, and toxic effects. The pharmacokinetics of taurine were studied in experiments on animals and humans (healthy volunteers and patients with heart failure II-III FC). When conducting experiments on animals, it was determined that after oral administration of taurine, 90% of the drug is excreted with bile, 10% with feces. With intravenous administration, 44% of taurine is excreted in 24 hours,

When taurine is administered intravenously to a healthy person, after 1 hour the level of the compound increases from 1.37 to 15.54 mg/100 kg, after 2 hours it decreases to 14.78 mg/100 kg. After 6 hours, the concentration of taurine in the blood approaches the control values. Taurine stays in the body longer when administered orally. Thus, when taurine is administered orally in the form of tablets to patients with heart failure in 20 minutes to food, already after 30 minutes there is an increase in the level of taurine in the blood by 17-18%. The maximum content of taurine in the systemic circulation was determined after 1.5-2 hours, the concentration of the drug in the blood is 19-70% of the dose and reaches 400, 410, 800 mmol/kg. A gradual decrease in the concentration of taurine is observed after 2; 4-5; 6.5-7 hours. After 24 and 30 hours, the level of taurine returns to the initial values. When determining the pharmacodynamics of taurine, it was established that it exhibits various clinical and pharmacological activity. Research on the neurotropic effect of taurine is devoted to studies of its influence on the activity of Na+-K+ and Mg2+-Ca2+ ATP-ases, cytoplasmic enzymes – NAD isocitrate dehydrogenase, L-glycerol-Z-phosphate dehydrogenase under hypoxia. The drug prevented a decrease in the activity of mitochondrial Na+-, K+-ATP-ase and Ca2+-dependent enzymes. Taurine is able to stimulate the growth of axons and the axoplasmic transport of macromolecules. Like GABA, taurine promotes the transmission of nerve impulses in synapses. Taurine at a concentration of 10-6-10-4 M suppresses K+ stimulated release of glutamine by affecting presynaptic Ca2+ L-type channels isolated by synapses of the cerebral cortex.

It has been established that taurine participates in the conduction of nerve impulses, normalizes the metabolism of nerve cells. Adding taurine to the diet of premature babies weighing less than 1300 g accelerates the development of the nervous system and improves the conduction of the auditory nerve. The stimulating effect of taurine on the impulse activity of different areas of the brain can be more pronounced than that of GABA.

For brain neurons, it is important to establish the role of taurine as a means of osmoregulation. A correlation was noted between the water content in the brain tissues and the level of taurine. Addition of taurine to the diet prevented morphological changes in the brain tissue and the development of cerebral edema and ischemia). Related to this are recommendations on the feasibility of adding taurine to basic therapy drugs (trental, cinnarizine, sedatives) in the treatment of patients with organic brain lesions of various genesis.

The drug helps to improve the cortical functions of the brain, memory, mental capacity, concentration of attention, and accelerate the reduction of neurological disorders. Taurine should be combined with vitamin preparations (pyridoxine hydrochloride, cyanocobalamin, preparations of adenyl nucleotides) to enhance the neurometabolitotropic effect. Due to the influence of taurine on the afferent and efferent links of the nervous regulation of the urinary bladder, it was reported about the feasibility of including taurine in the complex treatment of neurogenic bladder dysfunction in children.

The known property of taurine as a biologically active compound is to influence hormonal homeostasis: it reduces the level of thyroxine and triiodothyronine in the tissues of the thyroid gland. The hypoglycemic effect of taurine, as well as the effectiveness of taurine (taufon) intramamolar blockades in fibrocystic mastopathy, have been established. Taurine in the form of eye drops (Taufon drug) is widely used in ophthalmology. The drug has the ability to convert sulfhydryl groups into disulfide ones, normalize the metabolism of eye tissues, stabilize eye pressure, slow down the development of cataracts, myopathy, retinal dystrophy, and glaucoma.

Taurine is a necessary substrate for the normal functioning of the liver. The drug increases the synthesis of bile acids, stimulates glycolysis, gluconeogenesis has an antioxidant effect. When administered to rats in a dose of 100 mg/kg during acute hypoxia, taurine to a lesser extent in liver tissue than in brain tissue prevents a decrease in the activity of Na+-K+-ATP-ase and Ca2+-dependent enzymes. Important in the mechanism of action of taurine is the formation of a complex with lipocholic acid, which in its free state induces the oxidation of endogenous taurine.

The evidence is given in favor of the possible protective effect of taurine on the processes of oxidative stress, the activity of Krebs cycle enzymes, the level of calcium during experimental hypoxia, which claims the presence of an antihypoxic effect in the drug. The antihypoxic effect of taurine contributed to the use by obstetrician-gynecologists of a 4% solution of taufon parenterally to pregnant women during the last four days of pregnancy, which prevented hypoxic disorders of the fetal tissues, and was appropriate for delayed fetal development.

The following clinical and pharmacological properties of taurine can be stated:

1. The inhibitory neurotransmitter function contributes to the normalization of synaptic transmission, with the development of anticonvulsant activity.

2. Regulates the function of cell membranes, optimizing energy and electrolyte exchanges.

3. Regulates the function of the immune system, increasing the body's resistance to external negative factors.

4. Increases the contractile function of the myocardium, stabilizes the heart rhythm.

5. Stimulates the regenerative properties of tissues in case of damage and degenerative processes, in particular in the retina, blood vessels and liver.

6. Lowers the level of cholesterol in the blood.

7. Reduces the toxicity of other medications, in particular, cardiac glycosides.

A variety of clinical and pharmacological activity led to indications for the use of taurine for the treatment of degenerative disorders of the retina, diabetic cataracts, seizures caused by cerebral edema, chronic cardiovascular insufficiency, and disorders of the immune system. Continuation of research on the study of the clinical and pharmacological properties of taurine will allow to determine new indications for the use of this metabolic drug.

An important aspect of modern pharmacology is the purposeful search for compounds of the metabolic type of action that regulate energy homeostasis in the tissues of vital organs in various diseases and extreme situations. These drugs activate endogenous enzyme systems and contribute to the transport of exogenous metabolites and biometals into the cell. Amino acids, in particular, glutamic acid, are considered such physiologically active substances. The use of taurine (10-16 mg per day for 2-7 days) in pregnant women with a complicated course of pregnancy and on the eve of childbirth helps to improve the condition of the fetus and the course of the period of early neonatal adaptation in the newborn child. Taurine, included in the complex therapy of hypoxic-ischemic damage to the nervous system in newborn children, contributes to more effective dynamics of the elimination of the pathological process.

REFERENCES

Belenichev, I. F., Chekman, I. S., Shah, F., Nagornaya, E. A., Gorbacheva, S. V., Gorchakova, N. A., Bukhtiyarova, N. V., & Reznichenko, Y. G. (2020). Thiol-disulfide system: role in endogenous cyto- and organoprotection, pharmacological modula- tion pathways. Kiev : LLC Publishing House «Euston». 232 p. (Ru)

Belenichev, I. F., Cherniy, V. I., Kolesnik, Y. M., Pavlov, S. V., Andronova, I. A., & Abramov, A. V. (2009). Rational neuroprotection. Donetsk : Zaslavskiy AYu. (Ru)

Belenichev, I. F., Cherniy, V. I., Nagornaya, E. A., Pavlov, S. V., Cherniy, T. V., Gorchakova, N. A., Bukhtiyarova, N. V., Andronova, I. A., & Kucherenko, L. I. (2014). Neuroprotection and neuroplasticity: monograph. Kiev : Polygraph Plus LLC. 512 p. (Ru)

Belenichev, I. F. (2013). The role of heat shock proteins in the implementation of molecular biochemical mechanisms of neuroprotection. *Pharmacology and Medical Toxicology*. № 6(36). P. 72–80. (Ru)

Belenichev, I. F., & Bila, Y. V. (2017). The relationship between the concentration of HSP 70 activity of the thiol-disulfide system and the degree of neurological disorders in the modeling of acute cerebral ischemia. *Bulletin of Problems of Biology and Medicine*. № 1(135). P. 86–91. (Ru)

Belenichev, I. F., & Demchenko, A. V. (2015). Poor evaluation of the effectiveness of current neuroprotective agents in experimental chronic cerebral ischemia. *Zaporozhye Medical Journal*. № 2. P. 37–41. (Ukr)

Belenichev, I. F., & Litvinenko, E. S. (2015). Influence of modulators of the glutathione system – selenase and glutoxim on the energy metabolism of the brain in conditions of experimental acute cerebrovascular accident. *Pharmacology and Medical Toxicology.* № 6(46). P. 41–46. (Ru)

Belenichev, I. F., Gorbacheva, S. V., Demchenko, A. V., & Bukhtiyarova, N. V. (2014). The thiol-disulfide balance and the nitric oxide system in the brain tissue of rats subjected to experimental acute impairment of cerebral blood flow: The therapeutic effects of nootropic drugs. *Neurochemical Journal*. № 8(1). P. 24–27. URL: https://doi.org/10.1134/s181971241401005x (Ru)

Belenichev, I. F., Kolesnik, Y. M., Pavlov, S. V., Sokolik, E. P., & Bukhtiyarova, N. V. (2012). Malate-aspartate shunt in reactions of neuron adaptation to ischemia conditions: molecular-biochemical mechanisms of activation and regulation. *Neurochemistry*. № 29(1). P. 1–28. (Ru)

Belenichev, I. F., Litvinenko, E. S., & Subacheva, T. I. (2016). Markers of protein oxidative modification and nitrosating stress in experimental ischemic stroke and pharmacological modulation of the glutathione system. *Pharmacology and Medical Toxicology*. № 2. P. 30–36. (Ru)

Belenichev, I. F., Lytvynenko, E. S., & Kamyshnyi, A. M. (2018). The mrna expression character of HIF-1α And HIF-3α, nitrotyrosine, cGMP and interleukins in the Mongolian gerbils brain with acute ischemia during the glutathione system modulators therapy. *Bulletin of Problems Biology and Medicine*. № 1.1(142). P. 103–108. URL: https://doi.org/10.29254/2077-4214-2018-1-1-142-103-108 (Ru)

Belenichev, I. F., Mazur, I. A., Abramov, A. V., Kucherenko, L. I., Bukhtiyarova, N. V., Egorov, A. A., Belenicheva, O. I., & Polyakova, E. N. (2013). The endothelium-protective effect of 3-methyl-1,2,4-triazolyl-5-thioacetate (s)-2,6-diaminohexanic acid (lysinium):

Effects on the expression of vascular endothelial growth factor (VEGF) and the characteristics of the endotheliocytes of the cerebral vessels of animals with cerebral ischemia. *Neurochemical J.* № 7(4). P. 296–302. URL: https://doi.org/10.1134/s181971241304003x

Belenichev, I. F., Mazur, I. A., Kucherenko, L. I., Nagornaya, E. A., Gorbacheva, S. V., & Bidnenko, A. S. (2016). The molecular and ultrastructural aspects of the formation of mitochondrial dysfunction in the modeling of chronic cerebral ischemia: The mitoprotective effects of Angiolin. *Neurochemical J.* № 10(2). P. 131–136. URL: https://doi.org/10.1134/s1819712416010025

Belenichev, I. F., Pavlov, S. V., & Kucherenko, L. I. (2014). Neuro and mytoprotective effects of Angiolin and Cerebrocurin. *Pharmacology and Medical Toxicology*. № 3. P. 3–11. (Ru)

Belenichev, I. F., Yasinskiy, R. N., & Litvinenko, E. S. (2014). The changes of oxidative status markers in patients with newly diagnosed HIV/AIDS-associated lung`s tuberculosis after the course of treatment. *J. of New Medical Technologies*. № 21(3). P. 135–139. URL: https://doi.org/10.12737/5919 (Ru)

Bielenichev, I. F., Vizir, V. A., Mamchur, V. Y., & Kuriata, O. V. (2019). Place of tiotriazoline in the gallery of modern metabolitotropic medicines. *Zaporozhye Medical J.* № 21(1). URL: https://doi.org/10.14739/2310-1210.2019.1.155856 (Ru)

Chekman, I. S., Belenichev, I. F., Nagornaya, E. A., & Gorchakova, N. A. (2016). Preclinical study of the specific activity of primary and secondary neuroprotective agents. Guidelines. Publishing House Euston. 82 p. (Ru)

Chekman, I. S., Belenichev, I. F., Demchenko, A. V., Bobrova, V. I., Gorchakova, N. A., Kucherenko, L. I., & Bukhtiyarova, N. V. (2014). Nootropics in a complex therapy of chronic cerebral ischemia. *Nauka Ta Innovacii*. № 10(4). P. 61–71. URL: https://doi.org/10.15407/scin10.04.061

Chekman, I. S., Belenichev, I. F., Gorchakova, N. A., Kucherenko, L. I., Bukhtiyarova, N. V., & Pogotova, G. A. (2014). Antioxidants: clinical and pharmacological aspect. *Ukrainian Medical Chronicle*. № 1. P. 22–28. № 1(99). P. 23–33. (Ru)

Chekman, I. S., Gorchakova, N. A., Frantsuzova, S. B., & Nagornaya, E. A. (2009). *Metabolic and metabolitotropic drugs in the system of cardio and organ protection.* 155p. (Ru)

Chekman, I. S., Gubsky, Y. I., & Belenichev, I. F. (2010). Preclinical study of the specific activity of potential neuroprotective drugs. Kiev : SPC of the Ministry of Health of Ukraine. (Ru)

Davtian, L. L., Korytniuk, R. S., Drozdova, A. O., Naumova, M. I., & Olifirova, T. F. (2022). MAGNESIUM IN DRUGS. *Proceedings of the XIX International Scientific and Practical Conference*. P. 594–607. URL: https://doi.org/10.46299/isg.2022.1.19

Di Petrillo, A., Orrù, G., Fais, A., & Fantini, M. C. (2021). Quercetin and its derivates as antiviral potentials: A comprehensive review. *Phytotherapy Research*. № 36(1). P. 266–278. URL: https://doi.org/10.1002/ptr.7309

Galenko-Yaroshevsky, P. A., Chekman, I. S., & Gorchakova, N. A. (2001). Essays on the pharmacology of metabolic therapy. M. : Meditsina. 240 p. (Ru)

Golosnaya, G. S. (2009). Neurosurgical aspects of the pathogenesis of hypoxic brain damage in newborns. M. : Medpraktika. 128 p. (Ru)

Kolesnik, Y. M., Chekman, I. S., Belenichev, I. F., Gorbacheva, S. V., Gorchakova, N. A., Bukhtiyarova, N. V., & Kolesnik, Y. M. (2013). Thiol-disulfide balance is a determining factor in neuronal resistance to nitrosating stress under conditions of cerebral ischemia (literature review). *Journal of NAMS of Ukraine*. № 19(1). P. 3–11. (Ru)

Kolesnyk, Yu. M., Chekman, I. S., Yakovleva, I. Yu., Belenichev, I. F., Abramov, A. V., & Gorchakova, N. O. (2012). Comparative analysis of the influence of taurine and piracetam on morphological changes in the rat brain during circulatory hypoxia. *Reports of the National Academy of Sciences of Ukraine*. № 8. P. 160–165. (Ru)

Shabalov, N. P., & Tsvelev, Y. V. (Eds.). (2004). Fundamentals of perinatology: textbook (3rd ed.). M. : MEDpress-inform. 40 p. (Ru)

Shaforostova, E. A., Gureev, A. P., Volodina, D. E., & Popov, V. N. (2022). Neuroprotective effect of Mildronate and L-carnitine on the cognitive parameters of aged mice and mice with LPS-induced inflammation. *Metabolic Brain Disease*. URL: https://doi.org/10.1007/s11011-022-01047-9

Virmani, M. A., & Cirulli, M. (2022). The role of L-carnitine in mitochondria, prevention of metabolic inflexibility and disease initiation. *International Journal of Molecular Sciences*. № 23(5). P. 2717. URL: https://doi.org/10.3390/ijms23052717

Voronina, T. A., Kraineva, V. A., Zolotov, N. N., Kotel'nikova, S. O., & Val'dman, E. A. (2022). The role of oxidative stress in hemorrhagic stroke and restorative effects of mexidol. *Zhurnal Nevrologii i Psikhiatrii Im. S.S. Korsakova*. № 122(8). P. 65. URL: https://doi.org/10.17116/jnevro202212208265

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