UDC 616.272.2/.7

Igor BELENICHEV
Dr. able of Medicine, Full Professor, Head of the Department of Pharmacology and Medical Formulation with Course of Normal Physiology (i.belenichev1914@gmail.com)
***ORCID:** 0000-0003-1273-5314*

Nadezhda GORCHAKOVA
Dr. able of Medicine, Full Professor, Bogomolets National Medical University (gorchakova.na21@gmail.com)
***ORCID:** 0000-0002-7240-5862*

Oleh KUCHKOVSKYI
PhD in Biology, Senior Lecturer, Department of Pharmacology and Medical Formulation with the Course of Normal Physiology, Zaporizhzhia State Medical University, Ukraine (olegk181@gmail.com)
***ORCID:** 0000-0002-0548-0029*

Victor RYZHENKO
Teacher Assistant, PhD in Biology, Department of Medical and Pharmaceutical Informatics and Advanced Technologies (ryzhenko.vp1@gmail.com)
***ORCID:** 0000-0003-3466-7148*

Iryna VARAVKA
PhD in Medicine, Director of Zaporizhzhia Regional Council Municipal Institution "Zaporizhsky Medical College"

Pavlo VARVANSKYI
Head of the Department Pharmacy, Industrial Pharmacy Laboratory Diagnostics of Zaporizhzhia Regional Council Municipal Institution "Zaporizhsky Medical College" (vinceslav@ukr.net)

Ella GOROVA
Candidate of Medical Sciences, Associate Professor, Associate Professor at the Department of Physical Education, Sports and Health of the Taurida National University named after V.I. Vernadsky (gorova.ella@tnu.edu.ua)
***ORCID:** 0000-0003-0259-5469*

DOI 10.33617/2522-9680-2022-4-5

To cite this article: Belenichev I., Gorchakova N., Kuchkovskyi O., Ryzhenko V., Varavka I., Varvanskyi P., Gorova E. (2022). Pryntsypy metabolitotropnoi terapii u pediatrychnii praktytsi. Kliniko-farmakolohichna kharakterystyka suchasnykh metabolitotropnykh zasobiv (chastyna 2). [Principles of metabolithotropic therapy in pediatric practice. Clinical and pharmacological characteristics of modern metabolithotropic agents (part 2)]. *Fitoterapiia. Chasopys – Phytotherapy. Journal*, 4, 5–29, doi: 10.33617/2522-9680-2022-4-5

PRINCIPLES OF METABOLITHOTROPIC THERAPY IN PEDIATRIC PRACTICE. CLINICAL AND PHARMACOLOGICAL CHARACTERISTICS OF MODERN METABOLITHOTROPIC AGENTS (PART 2)

Abstract

The authors in the article, based on their own research, as well as based on the results of other scientists, presented modern ideas about the molecular-biochemical mechanisms of antioxidant, anti-ischemic, anti-hypoxic, neuroprotective, cardioprotective, endothelioprotective action of modern metabolitotropic agents and their dosage forms. The article describes the mechanisms of action and pharmacological properties of such drugs and special dietary supplements as glutamic acid and its salts, estrogens and phytoestrogens, aspartic acid and its combined preparations, L-arginine, GABA, its derivatives and combinations based on it, D-gluconic acid and preparations based on it, glycine, glutoredoxin, N-acetylcysteine, tryptophan, methionine, carnosine, nicotinamide, succinic acid and its salts, bioflavonoids and thiotriazoline. The peculiarities of prescribing these drugs in pediatric practice are described. The article describes approaches to the development and creation of new metabolitotropic agents.

***Key words:** anti-ischemic, energizing, neuroprotective, endothelioprotective activity, amino acids, thiotriazoline, estrogens.*

Ігор БЄЛЕНІЧЕВ
доктор біологічних наук, професор, завідувач кафедри фармакології та медичної рецептури з курсом нормальної фізіології, Запорізький державний медичний університет, вул. Сталеварів, 31, м. Запоріжжя, Україна, 69035 (i.belenichev1914@gmail.com)
***ORCID:** 0000-0003-1273-5314*

Надія ГОРЧАКОВА
доктор медичних наук, професор кафедри фармакології та клінічної фармакології Національного медичного університету імені О.О. Богомольця, бульвар Тараса Шевченка, 13, Київ, 01601 (gorchakova.na21@gmail.com)
***ORCID:** 0000-0002-7240-5862*

Олег КУЧКОВСЬКИЙ
кандидат біологічних наук, старший викладач кафедри фармакології та медичної рецептури з курсом нормальної фізіології, Запорізький державний медичний університет, вул. Сталеварів, 31, м. Запоріжжя, Україна, 69035 (olegk181@gmail.com)
***ORCID:** 0000-0002-0548-0029*

Віктор РИЖЕНКО
кандидат біологічних наук, асистент кафедри медичної та фармацевтичної інформатики і новітніх технологій, Запорізький державний медичний університет, вул. Сталеварів, 31, м. Запоріжжя, Україна, 69035 (ryzhenko.vp1@gmail.com)
***ORCID:** 0000-0003-3466-7148*

Ірина ВАРАВКА
кандидат медичних наук, директорка комунального закладу «Запорізький медичний фаховий коледж» Запорізької обласної ради, Оріхівське шосе, 14, м. Запоріжжя, Україна, 69600

Павло ВАРВАНСЬКИЙ
завідувач відділення фармакології комунального закладу «Запорізький медичний фаховий коледж» Запорізької обласної ради, Оріхівське шосе, 14, м. Запоріжжя, Україна, 69600 (vinceslav@ukr.net)

Елла ГОРОВА
кандидат медичних наук, доцент, доцент загальновузівської кафедри фізичного виховання, спорту і здоров'я людини, Таврійський національний університет ім. В.І. Вернадського, вул. Джона Маккейна, 33, м. Київ, Україна (gorova.ella@tnu.edu.ua)
***ORCID:** 0000-0003-0259-5469*

DOI 10.33617/2522-9680-2022-4-5

Бібліографічний опис статті: Бєленічев І., Горчакова Н., Кучковський О., Риженко В., Варавка І., Варванський П., Горова Е. (2022). Принципи метаболітотропної терапії у педіатричній практиці. Клініко-фармакологічна характеристика сучасних метаболітотропних засобів (частина 2). *Фітотерапія. Часопис*, 4, 5–29, doi: 10.33617/2522-9680-2022-4-5

ПРИНЦИПИ МЕТАБОЛІТОТРОПНОЇ ТЕРАПІЇ У ПЕДІАТРИЧНІЙ ПРАКТИЦІ. КЛІНІКО-ФАРМАКОЛОГІЧНА ХАРАКТЕРИСТИКА СУЧАСНИХ МЕТАБОЛІТОТРОПНИХ ЗАСОБІВ (ЧАСТИНА 2)

У статті автори на підставі власних досліджень, а також базуючись на результатах інших учених, представили сучасні уявлення про молекулярно-біохімічні механізми антиоксидатної, протиішемічної, антигіпоксичної, нейропротективної, кардіопротективної, ендотеліопротективної дії сучасних метаболітотропних засобів та їх лікарських форм. У статті описані механізми дії та фармакологічні властивості таких лікарських засобів та дієтичних добавок спеціального призначення як глутамінова кислота та її солі, естрогени та фітоестрогени, аспарагінова кислота та її комбіновані препарати, L-аргінін, ГАМК, її похідні та комбінації на її основі, Д-глюконова кислота та препарати на її основі, гліцин, глуторедоксин, N-ацетилцистеїн, триптофан, метіонін, карнозин, нікотинамід, бурштинова кислота та її солі, біофлаваноїди та тіотриазолін. Описано особливості призначення цих препаратів у педіатричній практиці. У статті описані підходи до розробки та створення нових метаболітотропних засобів.

***Ключові слова:** протиішемічна, енерготопона, нейропротективна, ендотеліопротективна активність, амінокислоти, тіотриазолін, естрогени.*

Glutamic acid actively participates in energy, protein and fat metabolism. With cardiovascular and renal pathology, stressful situations, its content in the tissues of the myocardium, liver, and brain decreases. One of the main aspects of the action of glutamic acid, related to its detoxification function – the ability to absorb toxic ammonia in the glutamine synthetase reaction (Zhang et al., 2022).

If we take into account that in hypoxic conditions, the content of ammonia in tissues increases, then the contribution of glutamic acid to the activation of oxidative processes, due to the binding of excess ammonia, becomes clear. Glutamic acid plays a leading role in transamination reactions. An increase in the activity of alanine and aspartate aminotransferases under the influence of glutamic acid in homogenates of the liver and thyroid gland of healthy rats, as well as in blood serum during hypoxia, is associated with the peculiarities of acid metabolism, because glutamic acid itself and its deamination product alpha-ketoglutaric acid play a role the same important role in metabolism as aminotransferase. The protective effect of glutamic acid is also due to its influence on biosynthetic processes in the adrenal glands. The analysis of experimental and clinical studies made it possible to conclude that

The antihypoxic effect of glutamic acid is realized with its influence, first of all, on the level of energy homeostasis and a change in the metabolic properties of mitochondria. A significant role is played by the transformation of glutamic acid in the regulation of mitochondrial energy exchange, since glutamate can serve as a source of the most energetically active substrate – succinic acid and trigger oxidative phosphorylation, and on the other hand, use energy and reducing equivalents in synthetic reactions (Zhang et al., 2022).

Thus, with hypoxia in organ tissues under the influence of glutamic acid, the level of ATP is more reliably normalized; subsequently, the oxidation of the most energetically efficient substrate of the Krebs cycle – pyruvic acid – is activated. The preventive effect of glutamic acid in conditions of hypoxia is also associated with an increase in the concentration of a-ketoglutaric acid, with the subsequent accumulation of oxalic acid in the tissues, which creates conditions for the involvement of lactate and other underoxidized products in the Krebs cycle. Prior administration of glutamic acid, during hypoxia, prevents the accumulation of lactic and pyruvic acids in the blood, keeps the glycogen content in the liver and muscles at a higher level. Glutamic acid is a source of substrates for a large number of intracellular enzymes, at the same time, the presence of the substrate protects mitochondria from death under denaturing influences. The introduction of glutamic acid into the body, in pathological conditions, activates glutamate dehydrogenase, malate dehydrogenase; causes a more economical consumption of carbohydrate, protein and fat substrates due to an increase in the level of reduced NADP or normalization of the NAD/NADP ratio.

The adaptogenic effect of glutamic acid was established in experiments in the simulation of hypoxic and hemic hypoxia. Thus, in acute hemic hypoxia, the use of glutamic acid contributed to a change in the oxidative phosphorylation reaction in the mitochondria of the liver and the cortical layer of the adrenal glands, which is manifested without the use of the drug in the process of adaptation to repeated hypoxia. The protective effect of glutamic acid is realized also on the basis of a change in blood oxygen saturation and an increase in its consumption by the body. In hemic hypoxia caused by the introduction of methemoglobin-forming agents, glutamic acid not only inhibits the formation of methemoglobin, but also significantly improves the respiratory function of hemoglobin by increasing the degree of its oxygen saturation. Glutamic acid is also effective in conditions of other types of hypoxia, which determined the expediency of including glutamic acid in the complex preparation Glutamevit, recommended in the conditions of the highlands, and other multivitamin complexes. The antihypoxic properties of glutamic acid are also due to the effect on the central and autonomic nervous system: this is facilitated by the participation of this drug in the synthesis of GABA, acetylcholine, potassium transport. The antioxidant activity of glutamic acid is associated not only with participation in the exchange of glutathione, the intensive transformation of the latter through succinic semialdehyde into beta-oxybutyric acid, lowering the cholesterol level by correcting the acid-base balance. It has been established that glutamic acid in doses of 50 mg/kg body weight of dogs enhances reflex responses arising in preganglionic nerves upon stimulation of the medulla oblongata and somatic nerves. It is assumed that its sympathoactivating effect is realized at the level of the medulla oblongata and spinal cord. At the same time, glutamic acid in doses of 10–100 mg/kg does not have a pronounced effect on the conduction of impulses in the upper cervical and other ganglia. The unique influence of glutamic acid on the metabolism of the myocardium determined the interest in its cardiotropic properties, the study in terms of anti-ischemic protection (Zhang et al., 2022). Researches in recent years indicate that glutamic acid supports the contractile function of the hypoxic and ischemic heart at a higher level and corresponds to its better recovery during the period of reoxygenation or reperfusion of the myocardium. At the same time, the

degree of ATP and acid phosphatase degradation during ischemia and hypoxia decreases, glutamate and aspartate deficiency in the myocardium is eliminated, glutamate and asparaginate formation is activated. Exogenous glutamic acid and products of its transamination enhance the anaerobic formation of ATP in mitochondria associated with the synthesis of succinate, thereby reducing the degree of myocardial contracture.

The stimulating effect of glutamic acid salts in hemic hypoxia, cardiovascular insufficiency of the hemodynamic type and glycoside intoxication on the content of adenyl nucleotides, creatine phosphate, nicotinamide coenzymes, activity of creatine phosphokinase, malate and lactate dehydrogenase in the rat myocardium was shown. The effect of glutamic acid on the cardio- and hemodynamics of dogs, as well as the mediators of the sympathetic nervous system involved in vascular regulation, was studied. Intravenous administration of glutamic acid (20–500 mg/kg) increases the stroke and minute volume of blood, increases the work of the left ventricle, and activates the sympathetic nervous system. The beneficial effect of glutamic acid on the cardiovascular system, the normalization of the heart rhythm in acute coronary insufficiency, was noted in an experiment on young and old animals, in particular, when potassium glutamate is administered. Intravenous administration of glutamates causes a significant stimulation of the collateral coronary blood supply of the ischemic myocardium, both due to the improvement of the blood supply and due to the activation of the energy metabolism of the transport of mono- and divalent cations. The compounds of calcium with glutamic acid were obtained and the synthesis of anesthesin glutamate for conduction and infiltration anesthesia was carried out. Calcium-magnesium salt of glutamic acid is recommended for the treatment of neuropsychiatric diseases and normalization of peripheral blood parameters. Methylorotate glutamate showed pronounced anti-inflammatory and regenerating effects. Double glutamates of the chelate type (disodium monocobalt glutamate) are erythropoiesis stimulators. Loglutam-1 and loglutam-2 glutamic acid preparations showed an antitumor effect.

The proposed mixture of potassium and magnesium glutamates was effective in arrhythmias complicating experimental myocardial infarction. This drug reduces the development of necrotic changes in the heart of rats when doses of isadrin are administered in toxic doses, although it has not been used in conditions of coronary insufficiency and ammonia intoxication. Biometals promote better absorption and transport of glutamate, as well as interaction with receptors.

The analysis of the literature showed that it is the combination of glutamic acid with other biometals that is of interest for further in-depth study. The low toxicity of glutamic acid salts (calcium glutamate, magnesium glutamate), their ability to form complexes with strophantin, digoxin and other biometals allow the emergence of new grounds for the use of glutamic acid and the creation of new highly effective drugs based on it.

In the 1990s, effective derivatives of glutamic acid were created, some of which entered the arsenal of medicines in the CIS countries. A derivative of glutamic acid – glutapyrone has anti-epileptic properties due to normalization of GABA-ergic processes and inhibition of oxidative stress. Glutamic acid decarboxylases have been proposed for the treatment of diabetes. Nooglutyl-N-15-oxynicotinoyl-L-glutamic acid combines tranquilizing and nootropic properties and is superior to piracetam in anti-anemic and anti-hypoxic properties.

The drug glutargin was developed on the basis of arginine and glutamic acid. Glutamic acid is used in the treatment of perinatal lesions of the central nervous system in order to improve brain metabolism (Shabalov & Tsvelev, 2004). Eltacin (L-glutamic acid + L-cystine) is taken 0.1 x 2 times a day sublingually between meals – a course of at least 2–4 weeks.

Estrogens. Recently, the mechanisms of the neuroprotective effect of estrogens have attracted the interest of clinicians, pharmacologists and physiologists. The largest class of sex steroids are estrogens. They secrete natural estrogens, synthetic estrogens, phytoestrogens and xenoestrogens. Natural estrogens are represented by such compounds as estrone, estradiol, estriol, which are present in humans and animals, and provide a whole range of physiological effects. Synthetic estrogens are artificially created compounds, mainly pharmaceuticals, with the aim of imitating the physiological action of hormones in case of their lack in the body or the need for excessive, predominant action. Phytoestrogens are chemical substances isolated from plants (isoflavones, umestanes, lignans) that have estrogen-like activity due to their structural similarity to human estrogens and have an affinity for beta-estrogen receptors. Phytoestrogens are found in many foods and plants, such as beans, grains, nuts, fruits, red clover, soybeans, and cimitsifuga. It is known that the root of cimitsifuga contains fractions capable of binding to estrogen receptors and inhibiting the cyclic release of luteinizing hormone in a negative feedback manner. Cimicifuga root extract causes the expression of estrogen receptors in the preoptic nucleus of the hypothalamus, while not affecting the uterus. Phytoestrogens are considered natural selective modulators of estrogen receptors, acting as estrogen agonists on the

cardiovascular system, bones, brain and as antiestrogens on the mammary gland and uterus. It is widely known that the direct effect of estrogens on organs and tissues is provided by a receptor-mediated way. Currently, various estrogen receptors (ER-α, ER-β), which are localized in various organs and tissues. Thus, ER-α is localized mainly in the ovaries, uterus, liver, kidneys, adrenal gland, macrophages, CD8-T-lymphocytes (suppressors), ventromedial and arcuate nuclei of the hypothalamus. ER-β – in the supraoptic and paraventricular nuclei of the hypothalamus, the hippocampus in the area of the CA1 and SAZ fields, the dentate gyrus, the neocortex, the basal nuclei, the olfactory bulbs, the nucleus of the bed of the terminal strip, the seam of the midbrain, the cerebellum, as well as in the lungs, intestines, and the urinary bladder, lymphoid tissue, fatty tissue. The localization of a large number of β-estrogen receptors in the brain indicates their significant role in the functioning of nerve cells and, as a result, the implementation of higher brain functions and the regulation of the vital activity of the entire organism, which determines the search for promising neuroprotectors among β-estrogen receptor modulators. Early experimental works of both domestic and foreign authors showed that estrogens exhibit neuroprotective activity in various pathologies of the central nervous system. It is known that a drug such as tamoxifen exhibits agonist/antagonist activity in a dose-dependent manner against α-ER and β-ER. It is known that a drug such as tamoxifen exhibits agonist/antagonist activity in a dose-dependent manner against α-ER and β-ER. In the course of experimental studies, it was established that the addition of an excess of glutamate (100 μM) tamoxifen in concentrations of 0.1 μM and 10 μM to a suspension of isolated neurons led to a significant decrease in the number of cells with signs of necrosis. Increasing the concentration in the tamoxifen suspension to 100 μM (Belenichev et al., 2014). The mechanism of action of tamoxifen in vitro studies is explained, in our opinion, in the limitation of transmitter autocoidosis due to increased affinity of GABA receptors. This is also confirmed by the studies of foreign authors, which suggest the dominance of the excitotoxic line of action of estrogens on the secretion of glutamate and the functioning of glutamate receptors in the neuroprotective mechanism. In particular, reducing hyperexcitability due to increased affinity of GABA receptors. In addition, estrogens reduce the manifestations of neuroinflammation by reducing the level of glutamate, which, in turn, is able to activate the transcription factor NF-kappaB, which is responsible for increasing the synthesis of pro-inflammatory cytokines. There are direct experimental data – estrogens prevent cell death in glial and neuron cultures caused by glutamine receptor agonists and LPS neurotoxins (toxins of gram-positive bacteria). Estrogen receptor modulators (only 17β-estradiol, 17α-estradiol does not work) interrupt LPS signal transduction from the plasma membrane to intracellular effectors and the cytoskeleton, and the estrogen receptor ER-α mediates the inhibition of nuclear translocation of the pro-inflammatory cytokine transcription factor NF-κB (Belenichev et al., 2014). The ability of tamoxifen and its metabolite to inhibit the neurotoxic system of glutamate and to exert a neuroprotective effect in β-amyloid amnesia is known. The study evaluated morphological changes in the neurons of the cortex, hippocampus, and forebrain, which are involved in the formation of cognitive status. It is shown that tamoxifen and 4-hydroxytamoxifen do not enhance glutamate-induced increase in intracellular calcium content and activation of NMDA receptors. In addition, tamoxifen and 4-hydroxytamoxifen blocked 17β-estradiol-induced glutamate-dependent increase in intracellular calcium concentration. At the same time, in culture media of hippocampal neurons, tamoxifen increased the expression of anti-apoptotic protein Bc1-2, which indicates the neuroprotective effect of the drug. So, tamoxifen and 4-hydroxytamoxifen partially exhibit the properties of ER agonists in the brain, and in the presence of 17 β-estradiol ("pure" ER agonist) they act as competitive ER antagonists. It is shown that the neuroprotective effect of SERMs is realized due to their positive effect on the endogenous cytoprotection factors of HSP and HIF-proteins (Belenichev et al., 2014). In our opinion, the ability of tamoxifen citrate to increase the content of Hsp 70 proteins in conditions of cerebral ischemia is due to its genomic and extragenomic effects. Our previous works, which are consistent with a number of experimental works of foreign researchers, have shown the ability of estrogens and SERMs to modulate the expression of global transcription factors responsible for the synthesis of Hsp proteins. In addition, SERM activation of β-estrogen receptors in the brain causes detachment from the last Hsp70-proteins, which ensures the entry of these proteins into the cell and the implementation of their biological function. The mechanism of this interaction is related to the role of Hsp 70 in maintaining the inactive state of estrogen receptors, not related to estrogens (Belenichev et al., 2014). Estrogens and their analogs reduce dystrophic processes in the placenta, improve its vascularization, and normalize utero-placental blood circulation. The following drugs are used: estradiol dipropionate – for the prevention and treatment of hypoxia, 20.000 units (2 ml of 0.1% oil solution) are administered intramuscularly every day for 15 days; folliculin – 5000 units intramuscularly every

day for 15 days; ϖSigetin, a synthetic estrogen-like drug, is administered intramuscularly to improve the vital activity of the fetus (2–4 ml of a 1% solution) or in the form of intravenous infusions of 20 ml of a 1% solution in 400 ml of 5% glucose. The course of treatment is 10 days. Sigetin improves the transport function of the placenta, increasing the permeability of placental vessels, has a selective antispasmodic effect on the vessels of the uterus, without affecting the general hemodynamics. However, the stimulating effect of the drug on the myometrium limits its use in premature pregnancy.

Aspartic acid has a positive effect on collateral coronary blood circulation in ischemic organs. The protective effect of aspartate in ischemia is associated with its rapid inclusion in tissue metabolism. Pronounced anti-amnestic effect is characteristic of drugs containing glutamic, aspartic, and methionine acids in various combinations with nicotinic acid. Prescribing a substrate-coenzyme complex for myocardial hypoxia, which includes preparations of individual amino acids – aspartic (panangin) and glutamic, as well as pyridoxal phosphate, led to the activation of the "malate shunt", a significant acceleration of the rate of elimination of ischemic damage indicators in acute ischemia of organs and tissues (Werner et al., 2022). The specificity of the neurotropic effect of aspartic acid is explained by the fact that enzyme systems for their synthesis and systems that ensure their release into the synaptic cleft under the action of certain stimuli are located in the synaptic endings. There are specific binding sites for the L-aspartic acid molecule on the postsynaptic membrane, as a result of interaction with which a physiological response occurs. There is a system of reuptake of these compounds that regulates their concentration in the synaptic cleft. Aspartic acid is included in composites for the correction of extrapyramidal insufficiency (Vitamixt-R, Aminocomposite-R, Aldarin, Aminopurinol). These composites contain a set of amino acids in different ratios: glutamine, aspartic acid, leucine, isoleucine, cystine and cysteine, etc. There are also other composites (Aminoven-R, Prove-R, Cerebron, Cevit), containing a set of amino acids in different ratios: α-alanine, glycine, glutamine, aspartic acid associated with magnesium, squalene, etc. Thus, the composite drug Prove-R contains a mixture of amino acids: glutamine, aspartic acid, ß-alanine, glycine. It increases the content of inhibitory neurotransmitters, stimulates energy metabolism, neutralizes toxic metabolic products, is widely used in neonatology for the treatment of perinatal encephalopathies. The daily dose is from 100 to 300 mg. Clinical application of composites – treatment of perinatal lesions of the central nervous system. Prove-R amino acid composite was used in the treatment of full-term children (40 weeks of gestation) with perinatal damage to the central nervous system. All children were admitted to the neonatal pathology department from the neonatal center at 2–3 weeks of life immediately after the completion of the complex of resuscitation measures. The age of the children of both groups, if they were included in the study, was comparable. The criteria for inclusion in the main and control groups were: an Apgar score of less than 5 points in the first minute after birth, ultrasound signs of hypoxic-ischemic damage to the brain in the absence of gross malformations (cysts of vascular plexuses, periventricular increase in echo density, periventricular cysts). Treatment was carried out in courses of 10 days with a 5-day break. The daily dose of Provita-R was 3 capsules (300 mg). The contents of the capsule were dissolved in water at room temperature and given to children three times a day before meals.

Arginine belongs to semi-substituted amino acids, it was first identified in 1886. In 1987, a group of English scientists led by Dr. Moncada showed that the endothelium-relaxing factor is nitric oxide. It is known that nitric oxide is the main compound in the regulation of vascular tone, microcirculation and other vital processes. The main source of nitric oxide is L-arginine (Shiraseb et al., 2021). Synthesis of NO occurs under the influence of three forms of NO synthetase (NOS): two constitutional-endothelialOh (eNOS) and neuronal (nNOS) and one induced (iNOS). The cycle of nitric oxide synthesis, catalyzed by NO synthetase, occurs within one iron-containing hemthiol center and includes a series of successive stages of arginine conversion, as a result of which, in addition to nitric oxide, citrullene is also formed. N-hydroxy-L-arginine is an intermediate primary product in the transformation of L-arginine under the influence of NO-synthetase. Next, N-hydroxy-L-arginine continues to be metabolized under the influence of superoxidants, generating nitric oxide. During the enzymatic oxidation of arginine by NO-synthase, the oxidizing agent is molecular oxygen. The intensity of the enzymatic synthesis of nitric oxide decreases with a decrease in blood oxygen saturation. It is believed that L-arginine binds to the protein globule near the iron-containing heme-thiol center and remains coordinated in this position until the formation of NO. The process takes place with the participation of NADP H and oxygen. During the complex oxidation reaction, catalyzed by the enzyme NO synthase, the enzyme attaches molecular oxygen to the terminal nitrogen atom in the guanidine group of L-arginine. The release of eNOS from the plasma membrane, the oxidation of L-arginine, and the synthesis of NO increase under the influence of receptor-dependent (acetylcholine, bradykinin, serotonin,

thrombin, ADP, glutamate, substance P) agonists that increase the concentration of calcium in the endothelium, but can decrease under the influence of receptor-independent calmodulin antagonists (trifluoropyrazine, calmidazole), hemoglobin, methemoglobin, alkyl and nitro derivatives of arginine (Belenichev et al., 2009–2019). The vasodilating effect of L-arginine, mediated by NO and, due to the ability of the latter to activate soluble guanylate cyclase and cGMP-dependent protein kinases, to reduce the interaction of calcium with the troponin-tropomyosin complex, plays a very important role in maintaining vascular tone, blood pressure, cardio and systemic hemodynamics. At the same time, the effect of other endothelium-dependent dilators (acetylcholine, bradykinin, histamine) is enhanced and inhibited by vasoconstrictors (angiotensin II, thromboxane A2), including the formation of endothelin – 1 release of norepinephrine by sympathetic nerve endings, the synthesis of endothelial growth factor, angiogenesis, inhibited proliferation, migration non-striated muscle cells, extracellular matrix synthesis. Manifestations of antioxidant, hypolipidemic, antithrombogenic, antiaggregant effects of NO are also possible, in addition, nitric oxide is involved in the regulation of breathing. In view of the data presented above, it is clear that the lack of NO leads to a violation not only of vascular tone, an increase in blood pressure. Later, it was established that the endothelium plays an important role not only in the regulation of tone, but also in growth processes, in the processes of leukocyte adhesion in the balance of profibrinolytic and prothrombogenic activity, and the main role is played by nitric oxide. Therefore, it is believed that the violation of NO bioavailability plays a key role in the dysfunction of the epithelium under the influence of risk factors, as a result of suppression of the expression/inactivation of endothelial NO synthetase (the enzyme responsible for the synthesis of NO from arginine) and a decrease in the synthesis of the NO precursor – L-arginine, a decrease in the density of receptors on the surface of endothelial cells, the irritation of which leads to the formation of NO; increasing the degradation of NO. Therefore, there are two main ways of increasing NO synthesis: increasing the concentration of L-arginine in the cell and increasing the expression of eNOS. Now there is a sufficient number of experimental and clinical works that confirm the feasibility of using L-arginine in diseases whose development is accompanied by a deficiency of NO. Thus, administration of L-arginine to experimental pulmonary hypertension in newborn premature rats increased the content of nitric oxide in the lungs and respiratory function. The drug has an antioxidant effect, but does not have a therapeutic effect after embolization, which was associated with the formation of peroxynitrite. L-arginine preparations not only have a positive effect on the course of hypoxia, but also contribute to the improvement of metabolic processes in brain tissue: causing a decrease in the content of products of oxidative protein modification and an increase in antioxidant protection systems and energy supply of mitochondria against the background of an increase in the level of nitrite anion in the brain. Arginine has antitoxic properties, which were associated with its physicochemical properties. Pronounced cationic properties of the guanidine group, prone to the complex formation of protons and the formation of seams with aldehydes, determined the influence on the processes of lipid peroxidation. In addition, arginine acts as the main supplier of urea, which is a free radical trap that are prone to the complex formation of protons and the formation of seams with aldehydes, determined the influence on the processes of lipid peroxidation. In addition, arginine acts as the main supplier of urea, which is a free radical trap that are prone to the complex formation of protons and the formation of seams with aldehydes, determined the influence on the processes of lipid peroxidation. In addition, arginine acts as the main supplier of urea, which is a free radical trap (Shiraseb et al., 2021). It should be noted the unidirectional effect of L-arginine and its derivative glutargin on the manifestations of hypoxia caused by keeping animals in a closed space and hemic hypoxia caused by gas. With these pathologies, the synthesis of nitric oxide in the liver decreased, the level of lipoperoxidation processes increased, and the activity of antioxidant and mitochondrial enzymes was suppressed. The curative and preventive effect of L-arginine and glutargan on the pathogenetic manifestations of hypoxic and hemic hypoxia was characterized by an increase in the level of nitric oxide synthesis, a decrease in the processes of lipid peroxidation, restoration of the function of the system of antioxidant protection and energy supply of mitochondria in the liver. With circulatory and hemic hypoxia, it was established that L-arginine significantly affects the synthesis of nitric oxide, processes of oxidative stress and antioxidant protection of brain mitochondria. Administration of L-arginine before the beginning of the reperfusion period contributed to the reduction of disturbances in the pro-oxidant-antioxidant state and normalized the activity of alanine and aspartate aminotransferases. The mechanism of this effect could be caused by the interaction of NO with oxygen forms generated during reperfusion, the main effect was the elimination of radicals, reduction of the cytotoxicity of the superoxide radical. L-arginine prevented the exhaustion of the body's antioxidant potential, which had a stabiliz-

ing effect on the membrane, limiting the penetration of free oxygen radicals into the hydrophobic layer. A direct protective effect of NO on the liver is possible, associated with suppression of the activity of Kupffer cells during reperfusion. Under the influence of endogenously formed NO, the conditions of microcirculation in the body improved in the post-ischemic period. Vasodilatation eliminated the adverse consequences of the phenomenon of lack of repeated improvement of blood circulation in the body. Nitric oxide can regulate oxygen consumption by cells and is involved in optimizing the metabolism of hepatocyte mitochondria in the reperfusion period, that is, the obtained facts indicated the important role of NO in the mechanism of the protective effect of L-arginine on the liver during the reperfusion system. The bactericidal effect of L-arginine was associated with the metabolism of the drug, which is metabolized separately from other acids contained in the wound. The conversion of L-arginine occurs both under the influence of NO-synthase (inducible and endothelial) and contributes to the transformation of L-arginine into L-citrullene. NO is synthesized with the participation of NO-synthase, has bactericidal and antitumor properties. When interacting with L-arginase, urea and L-proline can be formed, which is a substrate for the synthesis of collagen in tissues and polyamines (putrescine, spermecine, spermine). The latter play an important role in growth regulation, differentiation, DNA and RNA synthesis, which is necessary for tissue regeneration. Damage to peripheral nerves in neuropathic pain syndrome, as well as the inflammatory process in the joints in adjuvant arthritis, leads to sensitization of primary nociceptive effects and hyperactivation of central neurons of the pain sensitivity system. L-arginine plays a dual role in nociceptive brain processes, due to the formation of NO by means of NO-synthase, so it is possible with the involvement of NO in nociceptive reactions in the CNS and in the periphery. It is known that excitatory amino acids play a significant role in the hyperactivation of the central nervous system, due to the effect on NMDA receptors, but the latter can activate NO with increased production. At the same time, L-arginine is also a precursor of kyotrophin – an opioid dipeptide, which increases the release of metenkephalin in the spinal cord and brain, the latter has an antinociceptive effect in the brain and spinal cord. Thus, L-arginine had a preventive effect upon injury and transection of the sciatic nerve and the development of neuropathic pain syndrome in rats. Administration of L-arginine, against the background of a model neuropathic pain syndrome, reduced the degree of autotomy development. L-arginine had a beneficial effect on the course of ischemic damage in brain tissue, because NO in the nervous system plays the role of a mediator, modulator of nervous processes, participates in the regulation of immune protection of the brain, regulation of cerebral blood circulation in inflammatory traumatic and tumor diseases. Arginine improved cerebral blood circulation, although it did not reduce the ischemic zone. Arginine is not only a precursor of NO, it has an inhibitory effect on the development of atherosclerosis, blocking the activation and adhesion of leukocytes to the endothelium and the adhesion of platelets, the synthesis of adhesion proteins VCAM-1. The MCP-1 marker has an antiradical, antioxidant effect, inhibiting the synthesis of endothelin-1, preventing excessive accumulation of the extracellular matrix. The appointment of arginine to pregnant women with clinical and laboratory manifestations preventing excessive accumulation of extracellular matrix. The appointment of arginine to pregnant women with clinical and laboratory manifestations preventing excessive accumulation of extracellular matrix. The appointment of arginine to pregnant women with clinical and laboratory manifestation hypertensive disorders mild and moderate severity 1 g orally 3 times a day for 10 days. Proposed method of treatment hypertensive disorders in pregnant women with the use of arginine, it is possible to achieve normalization of the oxygen transport function of blood by inducing glycolysis and metabolic transformation of erythrocytes, which is accompanied by a decrease in their average volume, hematocrit and, accordingly, blood viscosity. As a result of these changes, fetoplacental hemodynamics is restored and, as a result, perinatal outcomes for fetuses and newborns improve (Abramchenko et al., 2011). The combined use of L-arginine and thiotriazoline is of interest. The pharmacological effect of the drug is due to a positive effect on the synthesis, transport and bioavailability of NO and the physiological functions of this molecular messenger. NO is an unstable, short-lived radical, and mechanisms such as the formation of stable S-nitrosol complexes with thio-containing low molecular weight compounds are provided for its stabilization and further transportation. In conditions of deficiency of thiol compounds (oxidative stress, ischemia, intoxication, hypertensive disease, etc.), NO transport is disturbed, because it is attacked by ROS such as superoxide radical and hydroxyl radical with transformation into a cytotoxic product – peroxynitrite. The drug increases the level of reduced thiols, in particular glutathione, with the help of activation of glutathione reductase and direct reduction of the oxidized thiol group. In addition, due to its antioxidant properties, the drug prevents the oxidative modification of NO by oxygen radicals. The drug is capable of acting as a NO transport molecule, forming nitrosothi-

ols. The drug also has a direct stimulating effect on NO synthase activity and NO production. Therefore, the combined drug has the unique properties of providing a protective effect in relation to the synthesis and transport of NO, its bioavailability, which is the basis of the mechanisms of cardio- and fetoprotection, has a uterolytic, antioxidant, membrane-stabilizing, angioprotective, hepatoprotective, anti-inflammatory and immunomodulatory effect. The combined drug exhibits pronounced cardioprotective and hepatoprotective properties due to the reduction of the destructive action of free radicals and the activation of the antioxidant system – superoxide dismutase and the glutathione link of the thiol-disulfide balance (glutathione, glutathione reductase, glutathioperoxidase). In addition, the combined drug has a cardioprotective and hepatoprotective effect due to the intensification of mitochondrial-cytosolic energy shunts, an increase in the level of ATP, an increase in the expression of nuclear transcription factors, anti-apoptotic proteins bcl-2, inhibition of apoptosis and necrosis. The drug improves blood supply to the heart, liver, pregnant uterus and fetus due to its endothelioprotective properties. The combined drug has a hypocholesterolemic effect. By suppressing the expression of pro-inflammatory cytokines IL-1b, it has an anti-inflammatory effect. The drug increases cellular and humoral immunity, increases the expression of interferons. Pharmacological properties NO-mimetic, vasodilating, uterolytic, cardioprotective, hepatoprotective, anabolic, energizing, antioxidant (Belenichev & Bila, 2017). There are data on the clinical effectiveness of the combined use of thiotriazoline and arginine. The duration of therapy is from 6 days to 3 months. 120 pregnant patients were examined. 44 with a threat of miscarriage and with delayed fetal growth against the background of standard therapy received a combination of thiotriazoline and arginine drugs (Tivortin). 46 pregnant women with a threat of miscarriage and fetal growth retardation – only standard therapy. And 30 pregnant women were without pathology and served as controls. The duration of therapy is 14 days. It was established that the inclusion of a combination of thiotriazoline and arginine in complex therapy reduced the risk of premature birth by 14.6%, as well as the risk of childbirth complications by 22%. All newborns whose mothers received combinations of thiotriazoline and arginine drugs did not differ from newborns on the Apgar scale and anthropometric indicators born from mothers of the control group. In the group of pregnant women with a threat of miscarriage and with fetal growth retardation, who received only standard therapy of newborns, had a significantly lower body weight (by 800 g) and a lower Apgar score (7.8 vs. 8.6 in the control group and in the group with thiotriazoline and arginine).

Gamma-aminobutyric acid was first synthesized in 1883, and only 67 years later in two independent laboratories it was established that it is found in large quantities in the brain. Even later, its biological role was determined. It has been established that GABA is the main inhibitory mediator in the nervous system. As a result of the study of the physiological properties of GABA and its metabolites, a wide range of its biological activity was established, in particular its participation in the regulation of blood circulation. Interest in GABA increased significantly when the receptors for which it is a ligand were discovered, as well as the involvement of the GABA-receptor complex in the action of many drugs that affect the functions of the central nervous system (CNS) (Bakhramov & Niyazov, 2022).

Ischemic and reperfusion lesions play a significant role in the structure of cerebral circulation disorders. It is known that in an ischemic stroke, the necrotic area of the brain is limited to a zone with a sharply reduced level of blood flow, which was called the penumbra. This zone is a potential target for pharmacological effects, because by affecting it is possible to limit the area of necrosis, restore blood flow and cell functioning.

In recent years, when discussing issues of brain protection, the term neuroprotection is used, which means the influence on a complex cascade of biochemical reactions that take place in the ischemic area. Considerable attention is paid to the role of excitatory neurotransmitter amino acids in the pathogenesis of ischemic and reperfusion lesions. This contributed to establishing the neurotoxic role of glutamic acid and increasing its level in ischemia. It was established the fact that, by influencing the so-called NMDA-receptors, glutamate promotes the activation of the influx of calcium into the cell, which contributes to its damage. Studies have established that GABA receptors and NMDA receptors in conditions of ischemia have an antagonistic effect on metabolic processes, which justify the use of GABA – active substances as antagonists of NMDA receptors and, accordingly, as neuroprotectors. Except this, GABA-mimetics actively influence the regulation of brain vascular tone, ensuring adequate perfusion. Back in the mid-60s of the 20th century, S.A. Mirzoyan and V.P. Hakobyan established the ability of GABA to increase blood circulation in the vessels of the brain, which is accompanied by a decrease in the tone of arteries and arterioles and almost no effect on venous tone, which is extremely important, since the outflow from the skull cavity does not worsen and does not increase brain edema. Receptors for GABA were detected in brain vessels, unlike extracranial vessels. Exog-

enous administration of GABA improves the functional state of neurons, although it is known that the blood-brain barrier for GABA is almost impenetrable. Only about 2% of GABA can penetrate the brain tissue. However, in ischemic, toxic, inflammatory processes, which are accompanied by an increase in the permeability of the blood-brain barrier, the level of exogenously administered GABA can significantly increase, although this is of an individual nature. The researchers explain the low permeability of GABA to the brain by the fact that, as a chemical compound, GABA is a non-polar molecule (zwitterion), which makes it lipophobic, that is, insoluble in lipids, which the blood-brain barrier is rich in.

Therefore, attempts were made to synthesize its derivatives, which would be able to penetrate through the BBB. Indeed, the condensation of GABA with nicotinic acid (picamilon) led to almost complete penetration of the molecule through the blood-brain barrier. Under the influence of picamilon, cerebral blood circulation improves, vasospasm in response to stress is inhibited. However, the interaction of picamilon with GABA receptors is lower than with GABA itself, which determines its effect mainly on blood circulation. In addition, the heterogeneity of GABA receptors was established. They are divided into A and B subtypes. It is the activation of type A GABA receptors that is accompanied by a neuroprotective effect. There is a modulation of the Cl current, which is accompanied by hyperpolarization of the membranes and voltage-dependent restriction of the influx of calcium ions into the cell. The neuroprotective action of piracetam is associated with the effect on GABA A receptors since the blockade of these receptors by bicuculline reduces its positive effect. Thus, the basis of the implementation of neuroprotection is the activation of GABA A receptors. For this, drugs that could freely penetrate through the blood-brain barrier are needed.

In the literature, there are reports that the level of GABA increases with ischemic brain damage (Bakhramov & Niyazov, 2022). This phenomenon is associated with the activation of GABA synthesis through Robert's shunt and inhibition of GABA A-dehydrogenase gene expression, which is homeostatic for brain cells, that is, in the process of evolution, nature developed a self-defense mechanism against stress. However, perhaps this is a species-specific phenomenon, since A. Green et al. (1994) did not find an increase in the synthesis of GABA in the brain tissue during occlusion of the carotid arteries. The authors conclude that brain ischemia does not enhance GABA ergic transmission. Although the selective agonist of GABA A-receptors muscimol shows a pronounced neuroprotective effect in the model of total (occlusion of carotid arteries), focal (method of microspheres and photochemical) models, but due to pronounced systemic toxicity, it is not used as a therapeutic agent. Therefore, despite the weak permeability of GABA through the BBB, it remains relevant as a treatment for disorders of cerebral circulation. As a medicine, GABA is used under the names aminalon, hamalon, GABA and is used in doses of 3–4 g per day. When using exogenous GABA in patients with cerebrovascular pathology, the neurological status improves, the manifestations of autonomic dysfunction decrease, and cognitive functions normalize. GABA is widely used in children's neurological practice because it does not exhibit toxic effects.

In the developing brain, GABA plays an important role in regulating the proliferation of neural progenitor cells, the migration and differentiation of new cells, the elongation of neurons, and the formation of synapses. By stimulating the production of somatotropic hormone, it regulates the growth and development of the child (Fine et al., 2014; Ben-Ari et al., 2012). As a medicine, GABA is used to treat some vascular diseases of the brain and belongs to nootropic drugs. GABA is not used for the treatment of pathological conditions and neuropsychiatric diseases caused by perinatal pathology, since its properties of preventing the death of GABA-ergic neurons in conditions of acute perinatal hypoxia are also unknown.

The most well-known GABA derivatives are 4-amino-3-(4-chlorophenyl) butanoic acid, the active substance of the drug baclofen, and 4-amino-3-phenylbutanoic acid hydrochloride, the active substance of the drug phenibut (noofen). Baclofen belongs to muscle relaxants, has a number of significant disadvantages, in particular, contraindications for atherosclerosis of cerebral vessels, cerebrovascular insufficiency, etc. Phenibut is a nootropic drug. Other properties of phenibut are also described. For example, it has a uterodepressant effect. Hypoxia during the neonatal period of development is one of the main causes of perinatal brain pathology in newborns, which often leads to infant mortality and disability in later ontogenesis. Obtained data on the neuroprotective and anti-ischemic effect of phenibut. In addition to the cerebral effects of GABA, attempts to use this amino acid in cardiovascular pathology deserve attention, as its cardioprotective properties have been established. In the development of disorders of the functioning of the cardiovascular system, the central component is of great importance. It has been established that stressors can contribute to the appearance of arrhythmias in practically healthy people and in people with functional disorders, and the use of GABA mimetic drugs contributes

to the normalization of the function of the cardiovascular system. Shown that the activation of stress-limiting systems prevents the violation of the contractility of the myocardium and its electrical stability. Intracisternal administration of GABA – a muscimol mimetic increases the threshold for the development of arrhythmias, which are provoked by stimulation of the hypothalamic area, and blockers of these receptors, on the contrary, contribute to the development of arrhythmias. It is believed that the antihypoxic effect of oxybutyrate is not related to the effect on GABA receptors, but to the metabolic effect on mitochondria, since the transformation of GABA in the body goes through the stage of succinic semialdehyde (a structural analogue of oxybutyrate) – Robert's shunt. It is known that succinic acid in conditions of ischemia/reperfusion is able to "monopolize" the respiratory chain of mitochondria without requiring oxygen (in conditions of its deficiency) for oxidation. Even more pronounced therapeutic effect in lithium oxybutyrate, the effects of normobaric hypoxia in rats on the 2nd day of life (a model of encephalopathy of premature babies) on behavior and learning ability were studied, as well as the possibility of correcting the detected disorders by introducing a derivative of GABA – salifene. It has been shown that the influence of hypoxia contributes to the increase of motor activity in juvenile age, and in the following periods worsens the ability to learn. Administration of salifene after hypoxic exposure eliminates behavioral disturbances. One of these GABA preparations is pantogam. Since 1995, it has been produced by the Russian company PIK-Pharma. According to its chemical structure, Pantogam is a calcium salt of D (+)-pantoyl-gamma-aminobutyric acid and belongs to nootropic drugs of a mixed type with a wide spectrum of activity, which determines its special place among medicinal products. Pantogam differs from other GABA-derived drugs in its balanced effect on the central nervous system. Due to the presence of the pantoyl radical in the pantogam molecule, the drug penetrates the blood-brain barrier and has a pronounced effect on the functional activity of the central nervous system. The pharmacological effects of pantogam are due to its direct effect on the GABA-receptor-channel complex. The drug also has an activating effect on the formation of acetylcholine, improves the utilization of glucose and blood supply to the brain, increases the brain's resistance to hypoxia, exposure to toxic substances, and stimulates anabolic processes in neurons. Pantogam is practically not metabolized in the body and is almost completely excreted within 48 hours. Pantogam is used in the treatment of neurological and mental diseases in children of various ages as monotherapy as well as in combination with other medicines. The combination of mild psychostimulant and moderately sedating effects of pantogam allows you to activate cognitive functions in children, reduces anxiety, and normalizes the child's sleep. The drug is well tolerated by children. At an early age, the use of pantogam in complex therapy is optimal for the earliest signs of psychomotor development delay (PMD), including for violations of the pace of pre-speech and language development from one year to three years. Possessing neurometabolic, neuroprotective and neurotrophic action, pantogam improves cognitive functions, increases mental activity and the scope of cognitive activity. Currently, there are two pharmaceutical forms of pantogam – tablets and 10% syrup (which does not contain sugar). The last form can be used in children from the first months of life. Pantogam syrup was prescribed to children aged 5–12 months. 0.5 g 2 times a day, in the morning and in the afternoon 15–20 minutes before meals for 56 days. All children were born to women with complicated obstetric and gynecological and somatic anamnesis. According to the outpatient charts, chronic intrauterine hypoxia was noted in all cases. A fairly high efficiency of pantogam in the form of 10% syrup in the treatment of psychomotor development disorders due to hypoxic damage to the central nervous system in children of the first year of life was found. Its good tolerability and safety have been shown. It was established that pantogam has a higher efficiency compared to cortexin and encephabol chronic intrauterine hypoxia was noted in all cases. A fairly high efficiency of pantogam in the form of 10% syrup in the treatment of psychomotor development disorders due to hypoxic damage to the central nervous system in children of the first year of life was found. Its good tolerability and safety have been shown. It was established that pantogam has a higher efficiency compared to cortexin and encephabol chronic intrauterine hypoxia was noted in all cases. A fairly high efficiency of pantogam in the form of 10% syrup in the treatment of psychomotor development disorders due to hypoxic damage to the central nervous system in children of the first year of life was found. Its good tolerability and safety have been shown. It was established that pantogam has a higher efficiency compared to cortexin and encephabol (Golosnaya, 2009).

D-gluconic acid (CH2OH(CHOH)4COOH) is a natural metabolite of mammalian cells and is formed in the body during oxidation of the aldehyde group of D-glucose. It is a substrate of the pentose phosphate pathway of glucose oxidation and, after phosphorylation, turns into the phosphoric ester of gluconic acid, which is an important product of cellular life. The phosphoroester bond is macroergic. Further transformations of phospho-

gluconate lead to the formation of pentoses, intermediate products of glycolysis and are accompanied by the accumulation of reduced phosphorylated pyridine nucleotides (NADP-H2). Thus, the pentose phosphate shunt is a supplier of metabolites for regenerative syntheses of plastic processes and energy metabolism.

The possibility of substrate activation of the pentose phosphate shunt of glucose oxidation deserves attention, although for a long time it was not considered as a source of energy supply to the myocardium in conditions of ischemia. However, it was recognized that its activity is highest in the conduction system of the heart, and it may have a certain value for maintaining glycolytic energy production, as a supplier of high-energy substrates: glyceralaldehyde-3-phosphate, fructose-1,6-diphosphate and fructose-6-phosphate. It was found that 2 hours after coronary artery occlusion, the key enzymes of the pentose phosphate cycle – glucose-6-phosphate dehydrogenase and 6-phosphate gluconate dehydrogenase – are activated in the ischemic and border zones of the myocardium, their activity remains elevated (20–30 times) for 10 days. The pentose shunt of glucose oxidation is responsible for the formation of reduced forms of NADP-H2, necessary for the restorative synthesis of fatty acids, steroids, adrenaline. In the reactions of fatty acid synthesis in conditions of ischemia, electrons can be accepted from NAD-H, which contributes to the prolongation of glycolysis.

Since NADP-H2 is a product of the functioning of the pentose phosphate shunt, the hypothesis of the replenishment of the macroerg pool due to the combination of the reactions of the pentose cycle with the reduction of pyruvate through a direct transhydrogenase reaction is supported by many researchers (Chekman et al., 2007–2019; Belenichev et al., 2009–2019).

Unloading of reduced equivalents is also possible during the direct transhydrogenase reaction. At the same time, the generation of ATP can occur while maintaining the conditions that allow the oxidation of NADH (36 mol of ATP per 1 mol of glucose that is oxidized). The pentose phosphate shunt enables the interconversion of hexoses and pentoses. Pentoses, which are produced in shunt reactions, are a substrate for the synthesis of nucleic acids, which contribute to the activation of reparative processes in the area of necrosis. When the enzymes of the pentose pathway of glucose oxidation are activated, the consumption of glucose-6-phosphate increases, while the activity of the key enzyme of glycolysis, phosphofructokinase, is reduced, which allows this pathway to be shunted, providing the substrate for further reactions. In this regard, the pentose phosphate pathway of glucose oxidation is very advantageous. It depends only on the presence of glucose-6-phosphate and the cytosolic pool of NADP-H2. These substrates are easily involved in synthetic processes that determine the efficiency of the shunt: CO2 is released early and resynthesis of 5 glucose-6-phosphate molecules out of 6 involved in the reaction occurs.

Thus, this pathway is practically autonomous and self-sufficient – only 1 molecule of glucose-6-phosphate is required from the outside. The established fact of energy supply by reactions of the pentose phosphate pathway of the sarcolemmal potassium-sodium pump deserves special attention. In the reactions of the pentose cycle, the main products that are involved in the glycolysis reaction are formed – fructose-1,6-diphosphate, glycerol-3-aldehyde, glucose-1-phosphate. Formation of fructose-1,6-diphosphate, saves 2 molecules of ATP. Studies of its effectiveness have been conducted by many researchers. The activity of the pentose phosphate pathway of glucose oxidation is greater in the conducting system of the heart, glandular and adipose tissue. In the conducting system of the heart, the energy generated during the operation of the pentose phosphate shunt ensures the functioning of ion pumps and maintenance of ion homeostasis of conducting cells.

Experimental and clinical studies have been conducted that established the antihypoxic and antitoxic properties of gluconates. The new domestic drug MEMBRATON is a bright representative of the indicated class of therapeutic and preventive means. The active components of the drug are gamma-aminobutyric acid (GABA) and magnesium compounds of gluconic acid. GABA and its metabolites have a wide range of biological activity, in particular, they are involved in the regulation of blood circulation. The receptors for which it is a ligand were discovered, as well as the participation of the GABA-receptor complex in the action of many drugs that affect the functions of the central nervous system (CNS). Gluconic acid belongs to a number of sugar acids obtained by oxidation of the aldehyde group of glucose. It is a substrate of the pentose-phosphate pathway of glucose oxidation. Phosphorylated form with macroergic connection gluconic acid is an important product of cellular activity. Further transformations of phosphogluconate lead to the formation of pentoses, intermediate products of glycolysis and are accompanied by the accumulation of reduced forms of phosphorylation of pyridine nucleotides (NADP H2). It is known that the pentose phosphate shunt is a supplier of metabolites for regenerative synthetic, plastic processes and energy metabolism. The role of the pentose phosphate cycle in ensuring the vital activity of cells is especially increased in the conditions of pathology – hypoxia, ischemia, inflammation,

oxidative stress, etc. It is difficult to overestimate the role of potassium and magnesium ions in maintaining electrophysiological properties, energy supply processes, implementing the systole-diastole cycle, maintaining vascular tone (blood pressure) and other vital processes.

Taking into account the above and data from the literature that cardiovascular and other pathologies are usually accompanied by magnesium deficiency in cells, it can be concluded that the use of the drug MEMBRATON, which is also a source of these ions, can be one of the pathogenetically justified approaches to exposure on metabolic processes, energy supply and ion homeostasis in pathologically changed cells of the myocardium, brain and other tissues and organs.

Given the fact that GABA derivatives do not penetrate the blood-brain barrier well, researchers turned their attention to gamma-oxybutyric acid (GABA) derivatives, which easily penetrate the CNS. The first such compound was sodium oxybutyrate, which activates hypothetical GABA receptors located on the DA-synthesizing neuron in prenatally alcoholic rats. As a result, cGMP activation, DA synthesis, and increased DA release occur. A similar mechanism was found in the derivative of glutamic acid – nooglutyl. Activation of GABA receptors leads to an increase in the transmembrane conductance of chlorine ions. Virtually all CNS neurons hyperpolarize under the influence of GABA due to an increase in the content of chlorine ions in inhibitory synapses. It is believed that GABA is responsible for medium-term inhibition in the cerebral cortex and hippocampus, in the subcortical nuclei, cerebellum, brain stem, as well as in the medulla oblongata and spinal cord. GABA-synthesizing neurons are more sensitive to hypoxia and other metabolic disturbances than other CNS neurons. Sodium oxybutyrate is similar in structure to GABA, but better penetrates through the blood-brain barrier. HOMK, which has a narcotic, sedative, hypnotic, muscle relaxant, antihypoxic, nootropic effect, is widely used in anesthesiology for non-inhalation anesthesia, for introductory and basic anesthesia, for postoperative psychosis, severe hypoxic conditions, in ophthalmology for primary open-angle glaucoma, in neurology and psychiatry with toxic and traumatic damage to the central nervous system, neurotic disorders, psychoses and sleep disorders, more sensitive to hypoxia and other metabolic disorders than other CNS neurons. Sodium oxybutyrate is similar in structure to GABA, but better penetrates through the blood-brain barrier. HOMK, which has a narcotic, sedative, hypnotic, muscle relaxant, antihypoxic, nootropic effect, is widely used in anesthesiology for non-inhalation anesthesia, for introductory and basic anesthesia, for postoperative psychosis, severe hypoxic conditions, in ophthalmology for primary open-angle glaucoma, in neurology and psychiatry with toxic and traumatic damage to the central nervous system, neurotic disorders, psychoses and sleep disorders, more sensitive to hypoxia and other metabolic disorders than other CNS neurons. Sodium oxybutyrate is similar in structure to GABA, but better penetrates through the blood-brain barrier. HOMK, which has a narcotic, sedative, hypnotic, muscle relaxant, antihypoxic, nootropic effect, is widely used in anesthesiology for non-inhalation anesthesia, for introductory and basic anesthesia, for postoperative psychosis, severe hypoxic conditions, in ophthalmology for primary open-angle glaucoma, in neurology and psychiatry with toxic and traumatic damage to the central nervous system, neurotic disorders, psychoses and sleep disorders.

Glycine. Previously, glycine, like GABA, was considered the main inhibitory mediator in the CNS of humans and animals, which inhibits, which was associated with specific glycine receptors, competitively and selectively blocked by strychnine and opens a chlorine channel in the synaptic membrane. In the late 1980s, the involvement of glycine in the positive regulation of NMDA receptors was proven. Later, it was found that glycine at submicromolar concentrations enhances NMDA-evoked responses of neurons in tissue culture. It was recorded that the value of NMDA-induced currents in neurons decreased in two cases: when isolated nerve cells were removed from the mother colony and when the perfusion rate of the culture increased. This is probably due to the fact that the cultured tissue secretes an unknown substance that potentiates NMDA responses quickly, which are removed or decayed in the above situations. After testing a certain set of compounds contained in the culture medium, it was determined that this "unknown" substance that enhances NMDA-induced currents is none other than the simplest amino acid – glycine. This effect of glycine is manifested in low concentrations (100–300 nM), which is approximately 10 times less than that required for activation of the inhibitory, strychnine-sensitive receptor. Later, similar results were obtained in experiments with neurons of the hippocampus, with granule cells of the cerebellum, neurons of the striatum. Activation of glycine sites is a necessary condition for the normal functioning of the NMDA-receptor-ionophore complex, which supports the hypothesis of glycine as a coagonist of NMDA-type VAK receptors.

With the introduction of matrix RNA from the primary rat brain culture into oocytes and the subsequent expression of genetic material, it was possible to study the process of NMDA receptor activation in an environment devoid of glycine. It turned out that under these

conditions, NMDA-induced responses occurred only when glycine was added to the medium.

These data confirmed that glycine is a co-agonist of the NMDA-receptor-ionophore complex, thus, the opening of the ion channel requires binding of the corresponding agonists to both glutamate and glycine recognition sites.

Glycine and its analogs can enhance neurotransmission mediated by NMDA receptors in brain tissue in vivo. It was found that D-serine enhanced neuronal excitation induced by microiontophoretic application of NMDA in the thalamus or in the red nucleus. Glycine also potentiated NMDA-evoked release of cGMP from rat cerebellar cells. However, in other experiments in vivo and on slices of brain tissue of adult rats, it was not possible to show the potentiating effect of glycine itself on NMDA-induced responses. These results suggest that the concentration of glycine under normal conditions is probably quite sufficient for full activation of the glycine site. However, another situation is quite possible – NMDA causes the release of glycine from neurons or glia to a level that saturates the glycine site. Glutamate and glycine recognition sites of the NMDA receptor-channel complex allosterically affect each other, changing the intrinsic activity of the agonist, but not its affinity. A partial agonist, occupying one of the recognition sites, causes such conformational changes of the entire receptor complex, which lead to an increase in the rate of formation of the complex of the second coagonist with the receptor. It is suggested that NMDA receptors exist in two conformational states – with an agonist preference and an antagonist preference. The role of glycine as a coagonist is that it converts the antagonist-predominant conformation of the receptor into the agonist-predominant one. The opinion is expressed that kynurenic acid also shifts the equilibrium in the direction of an increase in the proportion of the conformation that favors glycine occupying one of the recognition sites causes such conformational changes of the entire receptor complex, which lead to an increase in the rate of formation of the complex of the second coagonist with the receptor. It is suggested that NMDA receptors exist in two conformational states – with an agonist preference and an antagonist preference. The role of glycine as a coagonist is that it converts the antagonist-predominant conformation of the receptor into the agonist-predominant one. The opinion is expressed that kynurenic acid also shifts the equilibrium in the direction of an increase in the proportion of the conformation that favors glycine occupying one of the recognition sites causes such conformational changes of the entire receptor complex, which lead to an increase in the rate of formation of the complex of the second coagonist with the receptor. It is suggested that NMDA receptors exist in two conformational states – with an agonist preference and an antagonist preference. The role of glycine as a coagonist is that it converts the antagonist-predominant conformation of the receptor into the agonist-predominant one. The opinion is expressed that kynurenic acid also shifts the equilibrium in the direction of an increase in the proportion of the conformation that favors glycine that NMDA receptors exist in two conformational states – with agonist preference and antagonist preference. The role of glycine as a coagonist is that it converts the antagonist-predominant conformation of the receptor into the agonist-predominant one. The opinion is expressed that kynurenic acid also shifts the equilibrium in the direction of an increase in the proportion of the conformation that favors glycine that NMDA receptors exist in two conformational states – with agonist preference and antagonist preference. The role of glycine as a coagonist is that it converts the antagonist-predominant conformation of the receptor into the agonist-predominant one. The opinion is expressed that kynurenic acid also shifts the equilibrium in the direction of an increase in the proportion of the conformation that favors glycine. It should be especially noted that the participation of glycine is a necessary condition for the activation of the receptor complex, which allows considering the glycine-binding site as an element of the structure of the NMDA-receptor-ionophore complex, through which its pharmacological regulation is possible. It was established that the central inhibitory pathways have a glycinergic character. It is believed that glycine and strychnine are taken up with two different receptor sites, which, however, interact with each other. Glycine is used in connection with its nootropic, sedative and anti-alcohol effect, possibly in connection with the effect on alpha-1-adrenoceptors. There is limited experience in prescribing it to pregnant women with hypertension. There are well-known mixtures and vitamin complexes that include glycine. Glycine, like glutamic acid, is a neurotropic compound involved in biosynthetic processes, excretion of benzoic acid. Glycine is part of the drug Vicein for the treatment of senile, myopathic, radiation, contusion cataracts. It is also part of betaine, one of the components of acidin-pepsin tablets. Using the methods of system analysis, it was shown that glycine and its derivative N-acetylglycinamide have a distinct positive effect on the learning process. In order to enhance the neuroprotective effects of glycine, a composite dosage form was created that contains magnesium, glycine and GABA salts in experimentally substantiated ratios called Magnelong, and its neuroprotective effect in conditions of perinatal hypoxia and HPMC

was studied using the methods of system analysis, it was shown that glycine and its derivative N-acetylglycinamide have a distinct positive effect on the learning process. In order to enhance the neuroprotective effects of glycine, a composite dosage form was created that contains magnesium, glycine and GABA salts in experimentally substantiated ratios called Magnelong, and its neuroprotective effect in conditions of perinatal hypoxia and HPMC was studied Using the methods of system analysis, it was shown that glycine and its derivative N-acetylglycinamide have a distinct positive effect on the learning process. In order to enhance the neuroprotective effects of glycine, a composite dosage form was created that contains magnesium, glycine and GABA salts in experimentally substantiated ratios called Magnelong, and its neuroprotective effect in conditions of perinatal hypoxia and HPMC was studied (Belenichev et al., 2009–2019). A combination of glycine and thiotriazoline was developed and studied. The pharmacological effect of the combined drug is due to the mutually potentiating effect of thiotriazoline and glycine on the generation and transmission of impulses in excitatory and inhibitory synapses (due to the reduction of hyperexcitation of glutamate receptors and the increase in the activity of the inhibitory GABA-ergic system), as well as on the energy metabolism of the brain and detoxification processes. The combination of thiotriazoline with glycine increases the resistance of neurons to hypoxia by inhibiting the hyperexcitability of NMDA-glutamate receptors (potentiation of the Red/Oxi mechanism), as well as by increasing the GABA-ergic properties of glycine and increasing the concentration of GABA in the brain. The combination of thiotriazoline and glycine increases the resistance of neurons to hypoxia by increasing the functioning of the compensatory mechanisms of ATP production (GABA shunt). Due to its antioxidant properties, thiotriazoline strengthens the ability of glycine to reduce the sensitivity of a1-adrenoblockers of brain vessels to catecholamines and increases the central a1-adrenoblocking properties of the latter, which ultimately has a beneficial effect on the improvement of cerebral hemodynamics. The mutually potentiating effect of thiotriazoline and glycine will also be manifested in relation to the cognitive-mnestic function of the CNS (by increasing the energy of neurons and the expression of nuclear transcription factors). The drug is planned to be used for convulsive readiness in premature children.

N-acetylcysteine is a powerful antioxidant and, depending on the dose, suppresses oxidative stress in cells, including and nervous tissue. The ability of N-acetylcysteine to inactivate ROS and cytotoxic forms of NO, due to the formation of nitrosothiols, and also due to the reduction of iNOS expression, was revealed. The decrease in iNOS expression under the influence of N-acetylcysteine can be explained not only by its ability to bind ROS, which is involved in its expression, but also by the ability of glutathione formed from acetylcysteine to interrupt IL-1b-dependent mechanisms of expression of this enzyme (Belenichev et al., 2020). Unlike other precursors of glutathione, N-acetylcysteine easily enters mitochondria, especially against the background of its dysfunction, and leads to an increase in intramitochondrial glutathione. By normalizing the functioning of the nitroxidergic system of brain mitochondria by limiting the activity of NOS, by reducing its inducible form, acetylcysteine may inhibit NO-dependent mechanisms of neuroapoptosis in ischemia and hypoxia. The neuroprotective activity of acetylcysteine in conditions of perinatal alcoholization was revealed. It was established that the administration of acetylcysteine to rats that have undergone perinatal hypoxia leads to the inhibition of iNOS mRNA expression in the hippocampus and the sensorimotor zone of the cerebral cortex. The decrease in iNOS expression can be explained by the ability of N-acetylcysteine to bind ROS, which are involved in its expression (Belenichev et al., 2020). Also, the decrease in iNOS expression can be explained by ACC's ability to weaken the activation of the nuclear factor NF-κB, which controls the expression of apoptosis and cell cycle genes.

Glutaredoxin *(GRx-1)*. Glutaredoxin is one of the most important enzymes in the processes of disulfide reduction and deglutathionylation. Under conditions of oxidative stress, Grx participates in the process of S-glutathionylation, while when oxidative stress is reduced, it catalyzes the deglutathionylation reaction. Glutaredoxin carries out GSH-dependent reduction of oxidized cysteine residues (Cys – SOH, Cys – SO2H) in proteins, mediated by intermolecular disulfide bonds (-SS-) to the redox-active thiol state. Thiol-containing proteins are widespread in cells. These include enzymes of energy metabolism (phosphofructokinase, glyceraldehyde-3-phosphate dehydrogenase, α-ketoglutarate dehydrogenase, I complex of respiratory enzymes), enzymes of signaling cascades (protein kinase A, protein kinase Cα, protein tyrosine phosphatase 1b, protein phosphatase 2A), transcription factors (NFkB, HIF1, AP1) and many others. The oxidative shift in the redox potential of cells leads to the formation of disulfide bonds both within protein molecules and between proteins, as well as between protein and glutathione. The formation of mixed glutathione-protein disulfides (S-glutathionylation) is considered as a regulatory redox mechanism that modulates the activity of thiol proteins and associated metabolic pathways, signal

transduction, and gene expression. However, long-term accumulation of oxidized and glutathionylated proteins is associated with the activation of apoptotic pathways in the cell. In the Grx system, electrons are transferred from NADPH to glutathione reductase, then to oxidized glutathione with the formation of HG, which, in turn, reduces oxidized glutaredoxin. Substrates for Grx are disulfides and mixed disulfides. Grx-catalyzed disulfide reduction can proceed in two ways – monothiol and dithiol with the participation, respectively, of one or two Cys residues in the active center. The restoration of mixed disulfides of proteins or glutathionylated proteins, which occurs by the monothiol mechanism, was named "deglutathionylation". The monothiol mechanism leading to deglutathionylation is perhaps the most general function of glutaredoxin. Glutaredoxin is an electron donor for ribonucleotide reductase, plays a role in cell differentiation/proliferation, has anti-apoptotic functions, along with the ability to reduce dihydroascorbate to ascorbate. All these reactions proceed according to the monothiol mechanism. Glutaredoxin plays an important role in protecting cells from apoptosis through various mechanisms. For example, the importance of glutaredoxin in regulating the redox status of the serine/threonine kinase Akt has been described by a GSH-dependent mechanism by dephosphorylation and inactivation of Akt. The inhibitory ability of glutaredoxin on ASK1 kinase activity is described. Glutaredoxin has an activating effect on transcription factors.

Thus, glutaredoxin makes a significant contribution to the antioxidant protection of cells from the destructive effects of oxidative stress, which causes the formation of intra- and intermolecular disulfide bonds in proteins, oxidation of functional SH groups with the formation of sulfonic acid and subsequent proteosomal protein degradation. Course therapy with a recombinant glutaredoxin drug leads to a statistically significant increase in the content of anti-inflammatory IL-4 in the brain of rats after perinatal hypoxia. Such an increase in IL-4 suppresses the pro-inflammatory activity of macrophages and their secretion of TNF-α and IL-1β. This is expressed in a significant decrease in the content of TNF-α under the influence of glutaredoxin. Changes in the ratio between anti-inflammatory and pro-inflammatory cytokines are described, the first limits the local inflammatory reaction in the ischemic penumbra zone, which increases the chance of the nerve cell to survive, and the second prevents the cytokine-mediated increase in the activity of inducible NOS. The latter is manifested in the reduction of hyperproduction of toxic derivatives of nitrogen oxide. Administration of glutaredoxin had a positive effect on the concentration of HSP70 proteins in the brain starting from the 1st day of life of animals that underwent perinatal hypoxia. A similar mechanism of action of glutaredoxin is due to its participation in the normalization of TDR and as a result of protein stabilization and activation of hsp70 gene expression in neurons under the action of the drug (Belenichev & Bila, 2017). Administration of glutaredoxin had a positive effect on the concentration of HSP70 proteins in the brain starting from the 1st day of life of animals that underwent perinatal hypoxia. A similar mechanism of action of glutaredoxin is due to its participation in the normalization of TDR and as a result of protein stabilization and activation of hsp70 gene expression in neurons under the action of the drug (Belenichev & Bila, 2017). Administration of glutaredoxin had a positive effect on the concentration of HSP70 proteins in the brain starting from the 1st day of life of animals that underwent perinatal hypoxia. A similar mechanism of action of glutaredoxin is due to its participation in the normalization of TDR and as a result of protein stabilization and activation of hsp70 gene expression in neurons under the action of the drug (Belenichev & Bila, 2017).

Methionine due to its mobile methyl group, it has a lipotropic effect, promoting the synthesis of choline, the insufficient formation of which is associated with disturbances in the synthesis of phosphatidylcholine. Participates in the formation of adrenaline, creatine, activates hormones, vitamins B1, C, B6. Methionine as a donor of methyl groups increases the detoxification potential of the liver, and it is used in toxic brain lesions, chronic alcoholism, hypoxic encephalopathy, as well as hypoxic encephalopathy of newborns (Chekman et al., 2009; Semina & Stepanova, 2015; Shabalov & Tsvelev, 2004).

Tryptophan, like the previous compounds, is an irreplaceable acid that is transformed into tryptamine, serotonin, and nicotinic acid in the body, is included in the biosynthesis of NAD and NADPH, and is a necessary intermediate for the normal functioning of the body's metabolic systems. Drugs with antidepressant, antiepileptic, hypnotic and hypotensive effects have been created on the basis of tryptophan. Tryptophan is part of combined drugs for the treatment of liver diseases and obesity. Tryptophan has an anti-ulcer effect, which may be associated with the activation of prostaglandin synthesis. Data were obtained on the pharmacological effect of the combination of tryptophan and thiotriazoline. The pharmacological effect is due to the mutually potentiating effect of thiotriazoline and tryptophan on the course of neurochemical processes, which lead to an increase in the synthesis of melatonin and serotonin. The combined drug is planned to be used for disorders of cognitive functions in hypoxic encephalopathy of new-

borns, as well as organic brain damage, for sleep disorders and cognitive disorders in epilepsy in children, as an anti-anxiety and vegetative-corrective agent as part of complex therapy.

Carnosine – beta-alanyl-histidine obtained in 1900 by V.S. Gulevich. The dipeptide is not included in protein structures in the same way as anserine (methylcarnosine) and glutathione (gamma-glutamylcysteinylglycine). Carnosine in human muscles contains up to 100 mg% of the mass of wet tissue and is one of the most important endogenous adaptogens from the group of dipeptides. Various carnosine derivatives have antioxidant activity due to inhibition of ROS generation. As a result, there are local reactions and deep changes in the cellular response, in particular, activation of cytoimmune reaction systems, stimulation of wound healing activity and adaptation to stress. Carnosine has a connection between antioxidant and radioprotective activity. The study of the role of carnosine components in metabolic reactions showed that alpha-histidine is a reserve for the synthesis of histamine, and beta-alanine is included in the synthesis of collagen and nucleic acids. The antioxidant properties of carnosine and its influence on the development of inflammatory reactions and immune status served as the basis for attempts to use it as a stimulator of regenerative processes. Carnosine is a powerful neuroantioxidant and protects neurons from excess ROS (Belenichev et al., 2016). Carnosine inhibits iNOS hyperexpression in hippocampal neurons during cerebral ischemia. Carnosine (100 mg/kg), which was administered to pregnant animals under the conditions of simulation of perinatal hypoxia, contributed to the inhibition of hippocampal neuron apoptosis, the preservation of neuron mitochondria, and the inhibition of oxidative stress in the brain of newborns (Belenichev et al., 2016).

Pharmacological properties of nicotinamide can be attributed to vitamin preparations of the metabolic type of action, because it, like no other metabolitotropic drug, has such a wide spectrum of pharmacological activity. The metabolic effect of nicotinamide is due to the fact that the drug represents a catalytically active group of nicotinamide coenzymes, which plays an important role in almost all energy-dependent processes. Nicotinamide, like its analogue – nicotinic acid, is vitamin PP or Bz, plays an important role in the vital activity of the body (Chekman et al., 2008). Nicotinamide is a prostatic group of nicotinamide coenzymes – codehydrase I (diphosphopyridine nucleotidesd – NAD) and codehydrase II (3-phosphopyridine nucleotide – NADPH), which transfer hydrogen and carry out redox processes. Dehydrase II is also involved in the transfer of phosphate. In the last three decades, nicotinamide coenzymes have attracted the attention of not only biochemists, but also pharmacologists and clinicians. This is due to their distribution in the tissues of the body, as well as participation in the energy and plastic exchanges of cells. The synthesis of NAD has been studied in the tissues of the liver, heart, and mammary glands, in Ehrlich's ascites cells, and in mitochondria (Chekman et al., 2007–2019).

Studies of the enzymatic cleavage of nicotinamide coenzymes allowed us to find four enzyme systems involved in the degradation of NAD. First of all, they include nucleosidase or NAD-glycohydrolase (NAD-hydrolase, NAD-ase), which breaks the nicotinamide-riboside bond in the NAD molecule, with the formation of free nicotinamide and adenoside-phosphatribose. Very high enzymatic activity of enzymes of lungs, spleen, brain, liver and heart of other mammals. Another no less important way of splitting nicotinamide coenzymes is catalyzed by pyrophosphatase, which is found in the liver, heart muscle, and brain and hydrolytically splits the NAD-pyrophosphate bond in the molecule with the formation of two mononucleotides – mononucleotide-amide-nicotinic acid and adenylic acid.

The content of nicotine coenzymes in tissues is different. Of all the tissues of the animal body, the highest content of nicotinamide coenzymes was found in the liver, followed by the heart, followed by the adrenal glands, kidneys, diaphragm, mammary gland, brain, spleen, pancreas, and lungs. In cells that function normally, NAD is usually in an oxidized state; NADP, on the contrary, under the same conditions is in a reduced form. This means the mechanism that oxidizes NAD-H predominates, and this mechanism of electron transfer is the main source of energy for cell function. In the case of NADP, on the contrary, reducing mechanisms prevail. This is also reflected in the spatial separation of enzymes inside the cell: NADP-H should be located in those areas of the cell where there is a strong regenerative potential, NAD – on the contrary. In many pathological conditions, there are significant changes both in the level of nicotinamide coenzymes and in the ratio of oxidative and reducing forms. In anoxia, provoked by an experimental violation of coronary blood circulation, there is a decrease, mainly, in NAD in the myocardium. With hypoxia of the myocardium and brain, in the liver and brain, the total concentration of pyridine coenzymes also decreases, their ratio changes towards the predominance of reduced forms. These changes are associated with a violation of the final stage of oxidation, as a result of oxygen deficiency and limiting the possibility of its use with hypoxia of the myocardium and brain, in the liver and brain, the total concentration of pyridine coenzymes also decreases, their ratio changes towards the predom-

inance of reduced forms. These changes are associated with a violation of the final stage of oxidation, as a result of oxygen deficiency and limiting the possibility of its use with hypoxia of the myocardium and brain, in the liver and brain, the total concentration of pyridine coenzymes also decreases, their ratio changes towards the predominance of reduced forms. These changes are associated with a violation of the final stage of oxidation, as a result of oxygen deficiency and limiting the possibility of its use (Chekman et al., 2008).

During the development of the embryo (2-week-old rats), the content of all nicotinamide coenzymes in the liver increases. The activity of nicotinamide mononucleotide – adenyltransferase – the enzyme that synthesizes NAD increases during embryonic and postnatal development. The concentration of NAD in human erythrocytes decreases with age, which is probably associated with a change in the permeability of cell membranes.

It should be noted that the effect of NAD on the coronary collateral circulation is similar to that of malate and is characterized by both an increase in this indicator and the contractile activity of the myocardium. It has been established that NAD is superior to Krebs cycle mediators in its effect on the contractile activity of the myocardium. The rationality of combining nicotinamide with cardiac glycosides in order to reduce their toxicity is reflected in the works. The effect of nicotinamide on various systems and organs may be associated with the processes of inhibition of lipid peroxidation (Chekman et al., 2008).

It should be noted that nicotinamide in small doses increases glucose utilization and activates glycogenase. In large doses, this effect is not realized in nicotinamide. It was further confirmed in the clinic that nicotinamide completely normalized the indicators of the intraperitoneal glucose tolerance test with the "diabetic type" (tolerance to carbohydrates). Nicotinamide is an inhibitor of (ADP-ribose) synthetase of beta cells of the pancreas. In studies on rats, nicotinamide prevents the development of alloxan diabetes. In type 1 diabetes, nicotinamide prolongs the period of remission.

Nicotinamide, which is a precursor of NAD, in large doses suppresses lipolysis in adipose tissue, synthesis and secretion of VLDL in the liver, reduces the level of VLDL and HDL in blood serum and increases the level of HDL. Both in doses calculated in milligrams and in large doses, nicotinamide exhibits a vasodilating effect. With a single parenteral, but not oral administration, the drug acts as a fibrinolytic.

It has been established that nicotinamide coenzymes are affected by neurotropic drugs (Chekman et al., 2008). Nicotinamide regulates electrogenesis of the brain, affects resting potential and spontaneous electrical activity, contraction of smooth muscles. The effect of nicotinamide on neuromuscular transmission in the cholinergic synapse, the structural synapse and the glutaminergic synapse was established. The interaction of nicotinamide with presynthetic receptors and the possibility of regulating the release of the mediator and at the same time correcting the oxidative metabolism of cells of the cerebral cortex were determined. The experiment established the expediency of including nicotinamide in treatment regimens for peripheral neuropathies in streptozoon diabetes. Due to the effect of the drug on GABA-ergic receptors, nicotinamide together with GABA significantly increases the speed of blood circulation in the brain of cats. The interaction of nicotinamide with benzodiazepine receptors of synaptic membranes is shown. The above explains the anticonvulsant effectiveness of nicotinamide in focal and generalized epileptic activity in the cerebral cortex. In this regard, nicotinamide is considered now as one of the possible endogenous ligands of benzodiazepine receptors. Its regulatory participation in stressful situations, hypoxia, and epilepsy has been proven. The anticonvulsant activity of both nicotinamide and its derivatives, which is realized due to activation of GABA-ergic systems and inhibitory control of GABA, has been determined.

The use of nicotinamide in premature rats reduced the intensity of oxidative stress and increased the activity of enzymes, both in the maternal body and in the lung tissue of the fetus. This indicates the possibility of using nicotinamide to prevent the development of membrane-destructive processes in the lungs of fetuses and newborns.

The ability of nicotinamide derivative – nicotinamide hypoxanthine hydroxide to change immune reactions in vivo and in vitro is determined. Thus, the substance enhances the reaction of blast transformation of blood lymphocytes and stimulates the production of lymphocytes (Chekman et al., 2008). Thus, the obtained results from the study of the cardio- and neuroprotective properties of nicotinamide allow us to conclude that nicotinamide causes a reduction in damage to mitochondria by free radicals and ROS, and accompanies the activation of antioxidant enzymes of defense systems. At the same time, the activity of NAD-H DH and NADPH-H DH increases most effectively. Physico-chemical studies also allowed us to identify NADP as one of the compounds that clearly reacts with nicotinamide. Nicotinamide forms complexes with cAMP, cholesterol, ornithine hydrochloride, aspartic and glutamic acids, which is of certain importance for determining antioxidant properties. Nicotinamide actively

forms complexes with cations of biometals, which are modulators of metabolic processes in the body.

The results obtained in previous studies regarding the normalizing effect of nicotinamide on indicators of energy metabolism, lipid peroxidation during the toxic effect on the myocardium of anthracycline antibiotics, explain the ways of realizing the protective effect of the drug. The complex-forming properties of nicotinamide contribute, on the one hand, to a smaller contribution of iron ions to the stimulation of lipid peroxidation during the administration of drugs, on the other hand, they support the protection of metalloenzymes, that is, they form a support for the energy supply of the myocardium for a better combination of heart muscle contraction processes.

The conducted research, given experimental own results and data from the literature, are the basis for substantiating the possibility of including nicotinamide in the treatment regimens of oncological and hematological diseases with anthracycline antibiotics, taking into account its protective and adaptive effect.

The above studies established the main patterns of intermolecular interactions of nicotinamide with biomembrane components. A group of bioligands that form the most specific complexes with this drug has been identified. The promoting role of iron in the activation of free radical processes is known, and the ability of nicotinamide to form complexes with iron has been established. It can be assumed that the molecular mechanism of action of nicotinamide in the body occurs due to intermolecular interaction with the components of biomembranes. The covalent bond between nicotinamide and the receptor is carried out, possibly with the help of a divalent metal (iron and copper), which facilitates the formation of the conformational state of the receptor and ion channels. The values of the stability constants of nicotinamide complexes with biomembrane elements and biometals allow receptor-induced reconstruction of biomembranes and the possibility of remote regulation of energy processes in organs and tissues under its influence.

Nicotinamide facilitates the maintenance of hemostasis and contributes to the normal functioning of the body and an adequate response to changes in the external and internal environment. The presented results of experimental studies and literature data confirm the possibility of a wider inclusion of nicotinamide in various treatment regimens for patients with one or another pathology, taking into account the protective and adaptive effect (Chekman et al., 2008).

Nicotinamide is part of the drug Cytoflavin, which is used as a neuroprotector in the intensive therapy of premature newborns. In the clinic, cytoflavin is used intravenously at a dose of 2 mg/kg per day after dilution in a 10% glucose solution in a ratio of 1:5. The drug was administered to premature infants with long-term (more than 48 hours) metabolic disorders according to the acid-base status (CLS) during 5 days, the rate of introduction of the obtained solution varied from 1 to 4 ml/h.

The use of Cytoflavin in children with extremely low and very low body weight with post-hypoxic myocardial damage and severe metabolic disorders leads to the normalization of KLS indicators within a day from the start of treatment ($p = 0.043$), the VE parameter to -3.0 ± 0.1 mmol/l ($p = 0.001$), lactate level up to 1.5 ± 0.2 mmol / l ($p = 0.001$) and pronounced cardio-neuro- and cytoprotective effect.

Cytochrome C, which is used in complex treatment of coronary artery disease and heart failure, is also included in the drugs of metabolic, cardioprotective, and antioxidant action. Antioxidants, which are natural for the body components of the respiratory chain of mitochondria, which participate in the transfer of electrons – cytochrome C and ubiquinone – have found practical application as cardioprotectors. Experimental studies have shown that cytochrome C enters the cell during hypoxia and contributes to the normalization of energy-producing oxidative phosphorylation. We have established that cytochrome C reduces the processes of peroxidation in the myocardium in rubomycin intoxication and pituytrin coronary spasm. Currently, a liposomal dosage form of cytochrome C is being developed, capable of providing greater bioavailability.

The natural protection of cells from excess ROS is provided by antioxidants, including two hydrophilic (ascorbate and glutathione) and two lipophilic (ubiquinone and α-tocopherol). Ubiquinone occupies a central place in the antioxidant system, its content in the myocardium is much higher than in all other organs. Ubiquinone is able to inhibit the processes of peroxidation in membranes and protect DNA and proteins from the destructive action of hydroxyl radicals. The potential effectiveness of ubiquinone was discovered more than 20 years ago.

Using a DMPO (5.5-dimethyl-1-pyrroline-M-oxide) spin trap, it was established that the rate of succinate-dependent generation of superoxide radicals in mitochondria isolated from the ischemic myocardium of rats receiving the hydrophilic form of ubiquinone was approximately 2 times lower, than in the control group, and this difference was statistically significant. Ubiquinone also reduces the degree of ultrastructural changes in the myocardium during ischemia.

The protective effect of ubiquinone is associated

with its ability to inhibit the processes of peroxidation in membranes activated during reperfusion. It is known that the content of membrane-bound ubiquinone in the mitochondria of various mammals has an inverse correlation with the rate of ROS formation, and long-term intake of ubiquinone with food increases the level of α-tocopherol in mitochondria and protects the mitochondrial membranes of elderly rats from oxidative stress. The obtained data, which showed an improvement in the functional state of mitochondria after reperfusion, are in good agreement with such ideas.

In general, the available data allow us to conclude that long-term use of ubiquinone increases the resistance of mitochondrial membranes to the action of oxidative stress and this is accompanied by the recovery of the contractile function of the heart after a period of total ischemia. The protective effect of the lipophilic form of the drug, shown earlier, is fully reproduced when using the hydrophilic form of ubiquinone.

Succinic acid is the most important participant in the Krebs cycle. Additional use of succinate activates the Krebs cycle and provides antihypoxic, antiischemic, cytoprotective, adaptogenic, actoprotective and antioxidant effects. Succinic acid provides an exceptionally high power of supplying electrons and protons to the mitochondria and increases the recovery of ubiquinone. The antihypoxic and antiischemic effect of succinic acid can be associated with the activation of succinate dehydrogen oxidation and the restoration of the activity of the key enzyme of the redox chain of mitochondria – cytochrome oxidase.

The combination of sodium succinate and cytochrome C is promising from the point of view of energizing and anti-ischemic action. Sodium succinate salts are effective in reducing metabolic intracellular acidosis due to intracellular oxidation with the replacement of one hydrogen molecule for sodium with the formation of bicarbonate. The drug exhibits energizing properties, increases the synthesis of ATP by mitochondria in conditions of ischemia. The antioxidant effect of succinates is realized due to the inhibition of the production of reactive oxygen species by the energy-producing reactions of mitochondria. The antioxidant effect of succinate is manifested in the reduction of oxidative stress products, in particular carbonylated proteins. The drug activates the synthesis of endogenous antioxidant – glutathione (Chekman et al., 2007–2019; Belenichev et al., 2009–2019). Stimulates erythropoiesis. When using low doses of about 50 mg/day, activation of the formation and action of adrenaline, norepinephrine, and dopamine can serve as the leading mechanism. Thanks to this action, succinate has psychostimulant, normothymic and antidepressant effects. A similar effect is most pronounced in ammonium succinate. Succinate is part of the drug Reamberin (Volodin et al., 2005). 40 newborns were administered intravenous Reamberin at a dose of 5 ml/kg (75 mg/kg/day of sodium succinate) for 5 days. The use of infusion solutions based on sodium succinate has a reliable cerebroprotective effect in newborns who have experienced perinatal hypoxia. The neuroprotective properties of Reamberin are most pronounced when it is used early in premature newborns (in the first 12 hours). Systemic antihypoxic and antioxidant effect of Reamberin allows to reduce the duration of ventilator and reduce the frequency of complications associated with its use. Reamberin reliably reduces the frequency of development of periventricular leukomalacia in premature newborns who require mechanical ventilation and intensive care. Recommendations for the use of Reamberin for the elimination of post-anesthesia depression in newborns: two-time slow infusion of Reamberin for 2 minutes IV at a dose of 2 ml/kg with an interval of 10 minutes after the first administration, which is performed 10 minutes before the end of the surgical intervention. The antioxidant activity of flavonoid substances, in particular, quercetin, is widely covered in the literature. Among bioflavonoids, quercetin ranks second in terms of antioxidant effect. The number and location of aromatic oxygroups in the ring of the flavonoid series is of particular importance. Thus, in the series mericetin – quercetin – kaempferol, which have, respectively, three, two and one oxy groups, kaempferol is the least active. The antioxidant effect of flavonoids, including quercetin, is due to their ability to "quench" OH and O2 radicals, which are formed as a result of peroxidation. Quercetin acts as a scavenger, eliminating peroxidation products, protecting the lipid bilayer of cell membranes from damage. Blocking of free radical lipoperoxidation of membranes by flavonoids is connected not only with their structural features, but also with the ability to interact with membranes and penetrate through their lipid layer. This property is most pronounced in quercetin. A number of its metabolites, such as 3.4-dihydroxyphenylacetyl acid and 3-hydroxyphenylacetyl acid, have the properties of "scavengers" of free radicals. In addition to neutralizing free radicals and stabilizing cell membranes, the antioxidant effect of quercetin is due to its ability to activate enzymes of the body's own antioxidant defense (catalase, etc.).

Thiotriazoline. Almost all diseases are accompanied by the development of oxidative stress in organs and tissues. At the same time, a large amount of reactive oxygen species (ROS) and nitrogen monoxide, free radicals and lipid and protein peroxidation products are

formed. An excess of ROS and NO in conditions of antioxidant deficiency leads to oxidative modification of lipids, nucleic acids, and proteins. Oxidative modification of protein fragments of receptors, ion channels, and synaptic structures of a neuron leads to a violation of the generation, formation, and conduction of a nerve impulse, disrupts synaptic transmission, and, as a result, to the deterioration of cell function. It is also known that under the influence of ROS in the cell, the expression of redox-sensitive genes is activated, some of which are necessary to protect cells from the toxic effects of oxidative stress, and others, with an excess of ROS, initiate apoptosis. Such a pathogenetic link as ischemia also makes a big contribution to the development of many diseases. Its direct consequence is a violation of the oxygen regime of the tissues, a sharp decrease in the aerobic production of ATP and its deficiency, the activation of anaerobic glycolysis and the formation of metabolic lactic acidosis, shifts in pH to the acidic side, which leads to a decrease in the activity of enzymes and the activation of many pathochemical reactions. Energy deficit inhibits the functioning of synapses, ion channels, passive permeability of membranes for Ca ++ increases. In the future, secondary mitochondrial dysfunction is formed, and mitochondria from the "power stations of the cell", which would produce ATP, become sources of ROS and proapoptotic proteins. A sharp decrease in aerobic production of ATP and its deficiency, activation of anaerobic glycolysis and the formation of metabolic lactic acidosis, shifts in pH to the acidic side, which leads to a decrease in the activity of enzymes and the activation of many pathochemical reactions.

Thiotriazolin is a domestic original drug.

Currently, the drug is widely used in Ukraine, and the interest of doctors in it is growing every year. Thiotriazoline is morpholinium-3-methyl-1,2,3-triazoline-5-thioacetate, which has membrane-stabilizing, anti-ischemic and antioxidant properties. Thiotriazoline enhances the compensatory activity of anaerobic glycolysis, activates oxidation processes in the Krebs cycle while preserving the intracellular ATP fund.

The drug activates antioxidant systems and inhibits the processes of lipid oxidation in ischemic areas of the myocardium, reduces the sensitivity of the myocardium to catecholamines, prevents the progressive decrease in the contractile function of the heart, stabilizes and reduces the areas of myocardial necrosis and ischemia, respectively. Improves the rheological properties of blood (activation of the fibrinolytic system). The mechanism of action of Thiotriazoline is due to the presence of a thiol group in its structure, which has high regenerating and antioxidant properties (the thiol group is a trap for ROS and free radicals, and with mitochondrial dysfunction, the thiol groups of the mitochondrial pore are oxidized, which leads to the formation of mitochondrial dysfunction, energy deficiency and apoptosis), as well as the ability of the molecule to activate the compensatory (malate-aspartate energy shunt during ischemia (Chekman et al., 2007–2019). Thus, Thiotriazoline affects key links in the pathogenesis of ischemic damage to target organs during perinatal hypoxia.

Main effects:

Antioxidant – consists of several mechanisms: direct – transfers oxygen free radicals and ROS to an inactive state, indirect – reactivates antioxidant enzymes – superoxide dismutase and glutathione peroxidase and protects endogenous antioxidants – α-tocopherol and glutathione from "overconsumption".

Antiischemic and energizing – strengthens ATP synthesis, normalizes the respiratory chain of mitochondria, increases the utilization of glucose, free fatty acids, and glycogen in cells, limits low-productivity glycolysis and prevents the development of lactic acidosis in cells, normalizes the work of enzymes of the Krebs cycle, and in conditions of subtotal ischemia activates the compensatory malate-aspartate energy shunt (more productive and safer than glycolysis).

Membrane stabilizing – preserves the integrity of cell membranes, protects membrane phospholipids from peroxidation, normalizes transmembrane processes, preserves the threshold sensitivity of membrane receptors.

Anti-inflammatory and immunomodulating – reduces the content of circulating immune complexes, limits their release of inflammatory mediators, reduces the expression of pro-inflammatory cytokines IL-1b, stabilizes the membranes of basophils, mast cells and eosinophils, increases the phagocytic activity of macrophages, increases the level of interferon.

Reparative – stimulates the regeneration of the epithelium, restores the microcirculatory channel, activates the protein-synthesizing processes.

Antiapoptotic – inhibits NO-dependent mechanisms of apoptosis, increases the level of the anti-apoptotic protein bcl-2.

Thus, Thiotriazoline:

Normalizes energy metabolism of cells

Inhibits inflammatory reactions

Inhibits oxidative stress and oxidative modification of cellular and subcellular structures

Stimulates tissue regeneration processes

Increases the effectiveness of basic therapy

Reduces the duration of treatment

Prevents the development of complications

Reduces ischemic tissue destruction

The ability of thiotriazoline to prevent the occurrence and development of cerebral vasodilatation and the increase of both local cortical and total blood flow was revealed, which indicates that this drug has a cerebrovascular effect. The activity of the reaction of lipid peroxidation significantly decreased. The content of malondialdehyde, diene conjugates and free fatty acids decreased. These changes are associated with the reactivation of the antioxidant enzymes superoxide dismutase, catalase, and glutathione reductase under the influence of thiotriazoline and with an increase in the amount of natural antioxidants, in particular endogenous α-tocopherol.

The properties of the drug allow it to be used in obstetrics for the treatment of some pathological conditions. In 2003, V.V. Bybik, a study was conducted on the topic "Pharmacotherapy of fetoplacental complex function disorders at the threat of termination of pregnancy in primiparous women of mature age with the help of thiotriazoline and Magne-B6". 162 women were examined. It was proved that the use of thiotriazoline in combination with Magne-B6 in the studied group of pregnant women contributes to the inhibition of the intensity of the processes of lipid peroxidation (reduction of the accumulation of diene conjugates and the intensity of biochemiluminescence by 30–35%) against the background of restoring the state of the body's antioxidant defense system (increasing the activity catalase and sulfhydryl groups almost 2 times).

The use of enterosorption with thiotriazoline in the mother-fetus-child system was tested. 270 children were examined at birth. To compare the effectiveness of this method of correction, the same indicators were determined in umbilical cord blood as in newborns of risk groups. It was revealed that only in 28.8% of cases there were manifestations of minor maladaptation in the form of CNS depression syndrome in the first 2–3 days of life and a slower recovery of the initial body weight. In 72.2% of children, the condition at the time of birth was considered satisfactory. Thus, the proposed correction scheme is effective, which significantly increases the chances of normal growth and development of newborns.

Recently, there has been a tendency to create nootropics not only on the basis of the original chemical substance, but also on the basis of combining a known nootropic with drugs that enhance its positive properties (antioxidant, anti-ischemic, mnemonic, etc.). Currently, 4 nootropic drugs are registered in the CIS countries and the European Union, which are a combination of piracetam with diazepam, orotic acid, cinnarizine and aminalon, as well as two drugs which are combinations of melatonin with valerian extract, aminalon, pyridoxine.

A promising direction in the field of creation of nootropics is the development of a drug (perhaps a combined one) that combines the nootropic effect with antioxidant and anti-ischemic action.

The combined nootropic Thiocetam meets most of the proposed requirements. Thiocetam is an original combined drug containing the base racetam – piracetam and the antioxidant thiotriazoline. Thiocetam successfully combines the nootropic, mnemonic, antihypoxic effect of piracetam with the antioxidant, anti-ischemic, adaptogenic effect of thiotriazoline. By the strength of the pharmacological effects listed above, Thiocetam significantly exceeds the effect of piracetam and thiotriazoline, which are used in monotherapy. Thiocetam is superior to the best-known drugs of this pharmacological group (picamilon, phenibut, mildronate, nicergoline, phenotropil) in terms of its nootropic, neuroprotective effect.

On the modern pharmacological market, there are a lot of drugs that can affect these processes, but it is very difficult to choose a drug that is able to fully affect the pathological processes occurring in the body, without causing negative side effects. There is no ideal neurometabolic cerebroprotector.

The problem of using nootropics in the acute period of cerebral is chemia hypertensive disorders pregnant women is associated with their ability to cause hyperexcitation in the cortical regions, as well as with an increase in the energy expenditure of neurocytes. In this regard, the search for combined drugs that relieve the side effect of piracetam in the form of lactic acidosis is promising.

The most accessible method of creating a safe, highly effective drug today is combinations of known cerebroprotectors (fixed multicomponent complexes). One of these drugs is Thiocetam. The composition of this drug includes a combination of piracetam and thiotriazoline. Thiocetam has antioxidant (increase in the level of catalase, decrease in the level of malonaldehyde and diene conjugates, decrease in the number of free radicals), membrane-stabilizing (regulates ion transport of Na+, K+, Ca++), lipid-stabilizing (decrease in cholesterol and LDL, increase in HDL), antiaggregation (reduces platelet aggregation) and immunomodulatory effect. Thanks to Thiotriazoline, which is part of Thiocetam, it has a membrane-stabilizing effect (preserving membrane fluidity, protecting phospholipids from oxidation, prevention of polarization of ion channels and normalization of ion transport, preservation of the threshold sensitivity of membrane receptors; protective effect in relation to K+-Na+-ATPase).

Thiotriazoline, which is part of Thiocetam, eliminates the side effect of piracetam in the form of lactic acidosis, therefore it can be prescribed in the acute period, unlike pure piracetam.

There is evidence that severe endotoxicosis associated with hypertensive disorders in pregnant women, Thiocetam is used in complex therapy. V.V. Simrok and V.S. Cherkasova conducted studies on the effectiveness of the use of the drug Thiocetam in the treatment of placental insufficiency and obtained positive results. The drug Thiocetam combines the active bases of piracetam and thiotriazoline, which has respectively nootropic, anti-ischemic, antioxidant and membrane-stabilizing effects. The above-mentioned properties of Tiocetam and information about its use in obstetrics served as the basis for conducting research aimed at evaluating the effectiveness of the drug in the prevention and treatment of preeclampsia. Thiocetam was prescribed in a dosage of 5 ml of the drug, diluted in 200 ml of 5% glucose solution, intravenously once a day for 3 days; then 1 tablet 2 times a day for 7 days. To obtain a conclusion about the effectiveness of treatment of placental insufficiency with the use of Tiocetam, the indicators of uterine-placental-fetal blood circulation were evaluated during ultrasound examination of the fetoplacental complex. In pregnant women with placental insufficiency, according to ultrasound diagnostics, an increase in the systolic-diastolic index was found in the uterine arteries, umbilical cord arteries, and middle cerebral artery of the fetus.

Thus, the use of neuroprotectors in the complex of intensive therapy of encephalopathy in patients with severe hypertensive disorders of pregnancy is necessary. According to studies conducted in various clinics of Ukraine and the CIS countries, the use of piracetam and thiotriazoline during pregnancy did not cause adverse reactions from both the mother and the fetus, moreover, a good therapeutic effect was noted in the form of improvement of fetoplacental blood flow.

Unfortunately, at the moment there are no data on the use of the new domestic drug Thiocetam for the treatment of hypertensive disorders in pregnant women and newborns who have experienced perinatal hypoxia. In view of the revealed positive qualities of each component of the drug separately and positive data on its use during pregnancy, it is necessary to conduct clinical trials of Tiocetam for the intensive therapy of newborns who have suffered perinatal hypoxia (Cherniy et al., 2007).

CONCLUSION

The intensive development of molecular pharmacology and biotechnology during the last two decades contributed to the establishment of the pharmacology of metabolic therapy as one of the leading directions of modern pharmacotherapy.

Linus Pauling (1974) repeatedly emphasized: “I believe that, in general, the treatment of a disease with substances that are contained in the body and vitally necessary for it should be given preference in comparison with the use of powerful agents, be it synthetic drugs or extracts from plants, which are able to give and almost always produce undesirable effects”.

Taking into account this provision is the most important factor in the prevention of “drug-induced illness”, which has grown into one of the most serious problems of modern clinical pharmacology.

The most actively experimental and clinical studies were conducted in the field of cardio- and neurotropic effects of metabolites and their analogues, which is due to the urgency of finding means for effective therapy of diseases of the heart and central nervous system.

However, it should be recognized that until now the pharmacology of metabolic therapy agents has not been separated into an independent section and clear enough criteria for preclinical (experimental) and clinical study of drugs of this type have not yet been formulated.

At the same time, the ideas of metabolic therapy, at the origins of which stood the school of the outstanding domestic pharmacologist A.I. Cherkes and his student I.S. Chekman, are developing. Treatment with metabolic and metabolitotropic drugs has its own specificity and can be carried out for a long time. At the same time, as a rule, there is no weakening of the effects of traditional medicines prescribed against the background of metabolic therapy. Usually, the range of doses in which the therapeutic effect of intermediates and endogenous bioregulators is manifested is quite wide, which determines the safety of their use. At the same time, it is important to emphasize that the choice of optimal doses that exclude the negative effect of “feedback” requires an individual approach and understanding of the essence of the therapeutic effect.

The use of these means in pediatrics can be especially useful for age-related disorders of metabolic processes. Among the positive properties of metabolic agents are their beneficial effect on the immune status and a mild general adaptogenic effect. Compounds of this type of action reduce or prevent unwanted effects of drugs by increasing the detoxification potential of the body. Metabolic pharmacotherapy more than other directions of medical interventions corresponds to the postulate “Primum non nocere”.

REFERENCES

Abramchenko, V.V., Kostyushov, E.V., & Scherbina, L.A. (2011). Antioxidants and antihypoxants in obstetrics. (Oxidative stress in obstetrics and its antioxidant therapy). Sankt-Petersburg. 400 s (Russ.).

Bakhramov, K.K., & Niyazov, L.N. (2022). Synthesis of 4-hydroxibenzoic acid derivatives with amino acids and their potential pharmacological properties. *The Austrian Journal of Technical and Natural Sciences*, (1–2), 24–27. Retrieved from: https://doi.org/10.29013/ajt-22-1.2-24-27.

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 modulation pathways. Kiev: "LLC Publishing House " Euston ". 232 p. (Russ.).

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

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. Kyiv : Polygraph Plus LLC. 512 p. (Russ.).

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), 72–80 (Russ.).

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), 86–91 (Russ.).

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*, 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), 41–46 (Russ.).

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), 24–27. Retrieved from: https://doi.org/10.1134/s181971241401005x (Russ.).

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), 1–28 (Russ.).

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*, 30–36 (Russ.).

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), 103–108. Retrieved from: https://doi.org/10.29254/2077-4214-2018-1-1-142-103-108 (Russ.).

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 Journal*, *7*(4), 296–302. Retrieved from: 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 Journal*, *10*(2), 131–136. Retrieved from: 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*, 3–11 (Russ.).

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. *Journal of New Medical Technologies*, *21*(3), 135–139. Retrieved from: https://doi.org/10.12737/5919 (Russ.).

Ben-Ari, Y., Khalilov, I., Kahle, K.T., & Cherubini, E. (2012). The GABA excitatory/inhibitory shift in brain maturation and neurological disorders. *The Neuroscientist*, *18*(5), 467–486. Retrieved from; https://doi.org/10.1177/1073858412438697.

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 Journal*, *21*(1). Retrieved from: https://doi.org/10.14739/2310-1210.2019.1.155856 (.Russ.).

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. (.Russ.).

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), 61–71. Retrieved from: 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), 22-28*, *1*(99), 23–33 (.Russ.).

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. 155 p. (i.Russ.).

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

Cherniy, V.I., Kolesnikov, A.N., Kolesnikova, V.V., Popkov, A.V., & Kolesnikov, N.E. (2007). Prospects for the use of neuroprotectors in the treatment of preeclampsia.. *News of Medicine and Pharmacy*, *10*(214), 8–10 (.Russ.).

Fine, R., Zhang, J., & Stevens, H.E. (2014). Prenatal stress and inhibitory neuron systems: Implications for neuropsychiatric disorders. *Molecular Psychiatry*, *19*(6), 641–651. https://doi.org/10.1038/mp.2014.35.

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

Semina, V.I., & Stepanova, Y.A. (2015). Perinatal Hypoxia: Pathogenetic Aspects and Approaches to Diagnostics (Review of Literature). Part I. *Medical Visualization*, *2*, 95–105 (Russ.).

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

Shiraseb, F., Asbaghi, O., Bagheri, R., Wong, A., Figueroa, A., & Mirzaei, K. (2021). Effect of L-arginine supplementation on blood pressure in adults: A systematic review and dose–response meta-analysis of randomized clinical trials. *Advances in Nutrition*, *13*(4), 1226–1242. Retrieved from: https://doi.org/10.1093/advances /nmab155.

Volodin, N.N., Rogatkin, S.O., & Ludovskaya, E.V. (2005). Treatment of children who have undergone perinatal hypoxia during early neonatal adaptation. *Questions of Gynecology, Obstetrics and Perinatology*, *1*, 20–25 (Russ.).

Werner, E.R., Fernández-Quintero, M.L., Hulo, N., Golderer, G., Sailer, S., Lackner, K., Werner-Felmayer, G., Liedl, K.R., & Watschinger, K. (2022). Essential role of a conserved aspartate for the enzymatic activity of plasmanylethanolamine desaturase. *Cellular and Molecular Life Sciences*, *79*(4). Retrieved from: https://doi.org/10.1007/s00018-022-04238-w.

Zhang, Y., Song, W., Lu, Y., Xu, Y., Wang, C., Yu, D.-G., & Kim, I. (2022). Recent advances in poly(α-L-glutamic acid)-based nanomaterials for drug delivery. *Biomolecules*, *12*(5), 636. Retrieved from: https://doi.org/10.3390/biom12050636.

Надійшла до редакції 27.09.2022
Прийнята до друку 14.11.2022

The authors declare no conflict of interest
Participation of each author in writing the article:
Belenichev I.F. – general guidance in preparing the article, summarizing the results of the analysis;
Gorchakova N.O. – analysis and generalization of data on metabolic cardioprotection;
Kuchkovskyi O.M. – description of the antioxidant mechanism of action of metabolitropic agents;
Ryzhenko V.P. – description of the mechanisms of endogenous cyto-cardio- and neuroprotective action of metabolic drugs;
Varavka I.P. – analysis and generalization of data on metabolitropic drugs in pediatric practice;
Varvanskyi P.A. – description of the mechanisms of energotropic effect of medicinal products;
Gorova E.V. – collection and analysis of the literature review, editing of the article.

Email address for correspondence with the authors: olegk181@gmail.com