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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

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თანამშრომლობითა და მისი პატრონაჟით

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

ТБИЛИСИ - НЬЮ-ЙОРК

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board and The International Academy of Sciences, Education, Industry and Arts (U.S.A.) since 1994. **GMN** carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

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GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией и Международной академией наук, образования, искусств и естествознания (IASEIA) США с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения.

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GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

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При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

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2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

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ავტორთა საყურადღებოდ!

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1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

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6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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NEUROCHEMICAL STATUS OF NITRIC OXIDE IN THE SETTINGS OF THE NORM, ISHEMIC EVENT OF CENTRAL NERVOUS SYSTEM, AND PHARMACOLOGICAL BN INTERVENTION

[1]Belenichev I., [1]Gorbachova S., [1]Pavlov S., [1]Bukhtiyarova N., [2]Puzyrenko A., [3]Brek O.

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Nitric oxide (NO) has a wide range of biological effects: it participates in the work of the central and autonomic nervous systems, in the functioning of the gastrointestinal tract and genitourinary system, in the activity of secretory tissues and respiratory organs, and in the regulation of the cardiovascular system. At high concentrations, NO can demonstrate cytostatic and / or cytotoxic activity, which indicates its role in the cell-mediated immunity system. This function determines the effect of NO on the initiation and progression of apoptosis. The synthesis of NO from L-arginine is carried out under the action of three main isoforms of the enzyme of NO-synthases (NOS): neuronal (nNOS), endothelial (eNOS) and inducible (iNOS). In active form, all three isoforms are homodimers with a molecular weight of 130 (iNOS), 135 (eNOS) and 160 (nNOS) kDa [1,2].

Survival processes of nerve tissue under the influence of physico-chemical factors are controlled by signaling pathways. The most important signal messenger is nitric oxide, which is involved in the implementation of neurotransmission, neurodegeneration, and cellular reactions to oxidative stress [3]. One of the main functions of NO is vasodilation (relaxation of vascular smooth muscle). It is quite difficult to study the generation of NO and its distribution in cells, since NO is a short-lived molecule (its lifetime is 5-10 seconds). Therefore, scientists often focus on NO-synthase (NOS), an enzyme that synthesizes NO from L-arginine. A lot of researchers are currently studying NO-controlled signal transduction pathways [4,5].

It is known that NO of endothelial origin is involved in the mechanisms of arterial hyperemia, as one of the vascular reactions to inflammation. An excess of NO can cause increased permeability of the vascular wall and enhance exudative reactions, and its deficiency activates the adhesion of leukocytes to the vascular endothelium and their emigration to the surrounding tissue. The inflammatory process is usually associated with an increase in iNOS activity, which is capable f forming high concentrations of NO [6]. However, the question of the role of NO (the one formed with the participation of other (neuronal and endothelial) NOS isoforms) in the mechanisms of inflammation in ischemia / reperfusion has not been sufficiently studied [7].

Cerebral ischemia evokes a complex set of biochemical and molecular mechanisms that subsequently impair neurological functions due to the separation of physiological processes and impaired neuron integrity. They are mediated by glutamate "excitotoxicity", ionic imbalance, the development of free-radical reactions. In addition, inflammatory reactions initiated at the neurovascular interface, as well as alterations in the dynamic connections between endothelial cells, astrocytes, and neurons, make a significant contribution to the pathogenesis of cerebral stroke. The formation of oxidative stress, which is an inevitable companion of nerve tissue ischemia, is inextricably linked to inflammation. In this case, a so-called vicious circle is formed – inflammation causes activation of signal transduction pathways that are sensitive to the redox potential, which enhances oxidative stress [8].

A significant role in the mechanisms of neuronal death during the development of the glutamate-calcium cascade belongs to NO-mediated mechanisms. The exposure of NMDA receptors, which occurs against the background of toxic concentrations of glutamate, causes a flow of calcium ions into the cell. This, in turn, causes the activation of the calcium-dependent isoform of NO-synthase and the active synthesis of nitric oxide, which brings damage neurons [9].

NO can also be neurotoxic primarily because of its oxidizing properties, which include its ability to induce the production of peroxynitrite, that is a highly destructive active form of oxygen. At the same time, there is evidence that it is neuronal NOS that forms NO, which causes and complicates damage to neurons, while endothelial NOS improves blood supply in the area of ischemic penumbra. This confirms the role of NO in damage and death of the neuron and indicates the specificity of NOS isoforms. In addition, the type and stage of stroke should be considered. It has been proved that in the initial stages of ischemia, the expression of constitutional calcium-dependent NOS, determined by transmitter autocoidosis, prevails [10-12].

Nerve cell death, under conditions of NO overproduction, begins with the mechanisms of activation of phospholipases, overproduction of hydroxyl radical, and modulation of the NMDA receptors. But in the delayed post-ischemic period – from 7-14 days with global ischemia and from 1 to 3 days with focal ischemia, NO overproduction is recorded as a result of the activity of inducible NOS activated glia, macrophages and neutrophils [13-15]. The independence of the inducible form of NOS from calcium enables prolonged maintenance of high activity of this enzyme. The expression of this form with hypoxia occurs after 6 hours, in contrast to the constitutional calcium-dependent NOS, which is associated with the later appearance of activated astroglia, macroglia, and inflammatory cells. In the focal form of ischemia, these NO producing cells are located in the penumbra, and in global ischemia, they are in the structures that are most in need of oxygen. In this regard, the study of the mechanisms of regulation of NOS activity is promising for the elaboration of a treatment strategy for acute cerebrovascular disorders. Scientific literature provides description of cases with positive results on limiting NOS hyperactivity by means of the administration of inhibitors, and it is indicated that the administration of the latter decreases the progression of cerebral ischemia [16].

Little is known about the fact why large doses of nitric oxide do not damage the cells in which they are formed. It is believed that this is ensured by the work of the superoxide dismutase (SOD) enzyme, which inactivates superoxide. These understudied facts indicate the need to expand knowledge of the physiological and biochemical properties of NO. It has been established that NO in the nervous tissue forms active derivatives: nitrosonium (NO +), nitroxyl (NO-) and peroxynitrite (ONOO-). It has been established that NO and its transmutation products – peroxynitrite (ONOO-), nitrosonium ion (NO +), nitroxyl (NO-), and diazotrioxide (N2O3) are the main factors of nitrosate stress. Throughout this process, NO interacts with metals (heme iron of hemoglobin, myoglobin, iron-containing enzymes, non-heme iron of iron-sulphurous proteins, copper and zinc of active centers of enzymes). Besides, there is an indirect interaction of

NO + (S-, N-, O-nitrosation) with thiol, phenolic, hydroxyl and amino groups of proteins. As a result of contact, cell destruction occurs: desensitization of receptors, inhibition of mitochondrial enzyme activity, and fragmentation of nucleic acids. NO, binding back to Fe3 + of the active center of catalase, inhibits in the initial and postischemic periodof focal brain ischemia. Excess NO suppresses heme enzymes of the mitochondrial electron transport chain [17–20].

Excessive NO in the post-ischemic period interacts with heme iron and paired thiol groups to form a dinitrosol iron complex (DNIC). It is known that DNIC is a stronger nitrosylating agent, compared to NO, and it interacts with protein thiols, histidine, aspartate, glutamine, methionine, cysteine, glutathione. As a result, N- and S-nitrosothiols are formed. Besides, the pathological role of DNIC in conditions of ischemia is determined by the fact that it irreversibly nitrosylates iron-sulfide clusters of mitochondrial proteins (NADH-ubiquinonoxy reductase, succinate-ubiquinonoxy reductase and cis-aconitase) [19-22]. There is evidence of the ability of DNIC to significantly reduce the activity of enzymes responsible for the regulation of thiol disulfide equilibrium in the cell — glutathione reductase, glutathione S-transferase, and glutathione peroxidase in neuron suspensions [23-25].

The nitrosonium ion (NO +) damages the nucleophilic groups of active thiols, amines, carboxylases, hydroxyls, and aromatic rings. NO+ is formed under adverse conditions of nitric oxide overproduction, with the participation of ferrous iron and oxygen. It is known that NO+ has reducing properties, ionotropic and lusitropic effect on the myocardium, lowers the threshold of convulsive readiness, but with lactic acidosis it demonstratesprooxidant properties in relation to thiol-containing proteins and amino acids. There is in vitro data that the addition of NO– donors to a suspension of neurons reduces the content of glutathione [26]. It has been found that NO disrupts the electrical activity of neurons and inhibits the activity of sodium channels. This multidirectionality of NO can be explained by its different concentration inside the nerve cell. With its increase, a toxic nitrite anion is formed. N2O3, as a source of NO +, has the properties of a nitrosylating agent and forms N-nitroamines with aliphatic and aromatic amines. The products of their transformation are factors in the alkylation of nucleic acids and the deamination of purines. When N2O3 interacts with cysteine, S-nitrosocysteine is formed, and the reaction with glutathione produces S-nitroglutathione (NO transport molecule) [27,28].

In neurons, there is a mechanism for the release of NO from S-nitrosoglutathion with the participation of glutamyltranspeptidase and the formation of S-nitrosocysteinil glycine as a producer of NO. Cystine, whichisreduced to cysteine, participates in the transport of S-nitrosoglutathion. Cysteine reacts with S-nitrosoglutathione and forms S-cysteine, which is involved in the rapid transfer of information, which determines the formation of neuron adaptations. These reactions are controlled by glutathione reductase and glutathione transferase. When they are inhibited, there is oxidative modification of low molecular weight thiols, homocysteine formation, and impaired transport of NO and its cytotoxic derivatives, which enhance the thiol oxidation [29].

The antioxidant system of the neuron is able to regulate NO transport, providing resistance of the nervous tissue to nitrosate stress. In the first minutes of ischemia, macrophage or exogenous NO inhibits oxidative phosphorylation in neuronal mitochondria due to reverse binding to mitochondrial cytochrome C oxidase. Inhibition of the electron transport of mitochondria leads to the accumulation of superoxide and the formation of peroxytitrite. Peroxynitrite synthesis is characteristic of cells with high activity of NO synthase and ROS producing enzymes (xanthine oxidase, NADH oxidoreductase, cyclooxygenase, lipoxygenase, electron transport chain enzymes) [30].

Nitric oxide and its derivatives play a significant role in the expression of heat shock protein p53. The p53 protein inhibits tumor growth and maintains the integrity of the genome, causes cell cycle arrest or apoptosis, induces the expression of Bax, Fas, p53AIP and other apoptogenic proteins, and passes into mitochondria itself during apoptosis. This may be one of the reasons for the release of reactive oxygen forms and for a decrease in the charge of mitochondria [31].

In experiments on the culture of pear-shaped neurons of the rat cerebellum, data on the accumulation of p53 upon death of nerve cells due to excess sodium nitroprusside were obtained. Bcl-2 is believed to suppress NO-induced increase in Bax protein expression. Under the action of nitric oxide on the cell, the level of intracellular Bcl-2 protein decreases. Perhaps this occurs owing to caspase-induced cleavage or p53-dependent inhibition of the expression of this protein [32].

The pro-apoptotic effect of nitric oxide is also determined by the induced increase in the expression of apoptogenic proteins Bax. Mitochondria are able not only to perceive the apoptotic signal from NO, but also to synthesize it themselves due to the presence of constitutive NOS in them, which is localized in the mitochondrial membrane (mNOS). It is similar to macrophage iNOS, but is expressed constitutively. It is not established whether mNOS can be considered a separate isozyme, or is it iNOS containing post-translational modifications. It is assumed that it participates in the regulation of apoptosis due to the effect of mitochondrial pore proteins on the thiol-disulfide balance in the nitrosation or oxidation reaction [33].

All of the above is the rationale for the search for effective neuroprotective drugs that can prevent negative processes in the nervous tissue by means of inhibiting the cytotoxic derivatives of NO and reducing the effects of the pathobiochemical cascade and nitrosate stress.

There is substantial evidence that irreversible changes in the area of ischemic damage can be stopped with the help of neuroprotective drugs that can reduce focal ischemia at the molecular and cellular levels, and correct its consequences [34-36]. A promising direction in the creation of new drugs are substances with a double mechanism of action. It is assumed that the best combination is substances that combine the properties of a “scavenger” of free radicals and a sodium channel blocker [37]. Summarizing the literature data, it can be stated that drugs with an antioxidant nature of action have evidence of their effectiveness, but more often hypothetically. This direction is the youngest and possibly promising in the neuroprotection section [38].

There is substantial evidence that irreversible changes in the area of ischemic damage can be terminated with the help of neuroprotective drugs that can reduce focal ischemia at the molecular and cellular levels, as well as correct its consequences [34-36]. A promising direction in the creation of new drugs is designing substances with a double mechanism of action. It is assumed that the best combination is reprsented by substances that combine the properties of a “scavenger” of free radicals and a sodium channel blocker [37]. Summarizing data from the scientific literature, it can be stated that drugs with an antioxidant nature of action generally prove their effectiveness, but more often it is hypothetical. This direction is the youngest and possibly promising in the neuroprotection investigations [38].

The nature of the effect of NO on various biochemical and

physiological processes is conventionally divided into direct and indirect. A direct effect is achieved by direct interaction between NO and biomolecules. The main target in this case is the heme iron of hemoglobin, myoglobin, guanylate cyclase, cytochrome P-450, NO synthases and other heme-containing proteins. NO also interacts with non-heme iron, which is part of iron-sulfur proteins and nucleic acids, and free iron (Fe_3^+). Nitric oxide inhibits Fe_3^+-mediated oxidative reactions and thereby shows an antioxidant effect. In addition, NO inhibits the processes of lipid peroxidation (LPO), obviously preventing their spread. The direct targets of NO are copper and zinc atoms, which are part of the enzymes, and high-energy free radicals (radicals with a carbon center, lipid radicals, and nitrogen dioxide ones). The direct effects of NO dominate the body under physiological conditions when this molecule is synthesized, mainly by constitutive forms of NOS in low amounts. At the same time, the concentration of NO in the tissues is 0.1-1 μmol, while that of O^2- due to its high superoxide dismutase activity is three times lower. Due to the direct action of NO, its regulatory and signaling functions are mainly implemented [39].

The indirect effect of nitric oxide is mediated through its reactive forms (RNOS), which are the product of the reaction of NO with O_2, O_2- or H_2O_2. Transition metals may also be involved in the formation of RNOS. The indirect effect of NO is manifested with an increase in its synthesis associated with iNOS induction, which is observed during inflammatory processes of various etiologies (when phagocytic cells are activated, the concentration of NO near them can reach 10 μmol) and is combined with an increase in the formation of reactive oxygen species (ROS) [40]. The indirect action of NO is realized through S-, N-, and O-nitrosation, in which the nitrosonium cation (NO^+) is attached to amines, thiols, or hydroxyl groups of aromatic compounds, through nitration carried out by attaching nitro groups (NO_2) to biomolecules (aromatic rings, in particular tyrosine ones, are the most sensitive to nitration), as well as through the oxidation or hydroxylation of biomolecules. As a result of these reactions, post-translational modifications of proteins occur, which play a significant role in the pathogenesis of acute and chronic diseases. The correlation between the mentioned types of bio-substrate modifications and their severity depend on the metabolic conditions, first of all, the redox potential, pH, and the balance between the formation of NO and ROS in the cell compartments [41]. These conditions are referred to as nitrosative and oxidative stress. The main reactive forms of nitric oxide, which, when excessively synthesized in vivo, cause the body to undergo nitrosative and oxidative stress, are diazotrioxide (N_2O_3) and peroxynitrite (ONOO-), respectively. But there are no clear boundaries between the indicated states, since N_2O_3, easily entering into S- and N-nitrosation reactions, is capable under certain conditions of participating in oxidative reactions, and ONOO- as a strong oxidizing agent can perform nitration and nitrosation of biomolecules. The direct and indirect action of NO in the cell compartments occurs simultaneously, but it is not uniformly expressed due to differences in the synthesis of NO and O_2-, and also because O_2- diffuses poorly through the membranes due to its charge [42].

Numerous studies have shown that in acute cerebrovascular impairment (ACVI), NO improves blood supply to the brain through vasodilation, decreased platelet aggregation and parietal adhesion of neutrophils, inhibits the activity of NMDA receptors and reduces the “excitotoxic” effect of glutamate. However, during reperfusion, the damaging effect of NO predominates, exacerbating the destruction of dying nerve cells [43].

Another very important aspect of the physiological role of NO is associated with its biological properties as a neurotransmitter, which is due to the lifespan of NO and the ability to diffuse from the synthesis site by 100 μm. NO is widely present in both the central and peripheral nervous systems. NO does not specifically bind to postsynaptic membrane receptors, as in cases with classical neurotransmitters, but it diffuses to other sites, including presynaptic neurons (i.e., acts as a retrograde messenger), as well as other adjacent neurons and glial cells. It is believed that NO acts probably as a neuromodulator, mediating the dynamic activity of neurons, rather than directly affecting the activity of their potentials [44].

At the same time, it has beendiscovered that NO can act as a neurotransmitter, mediating the effects of the so-called non-adrenergic and non-cholinergic neurons (NANC-neurons), which, along with the cholinergic and noradrenergic conductors of the autonomic nervous system, can represent the third type of nervous system [45]. The NO, which is produced as a result of iNOS activation, is primarily intended to protect the host organism; it contributes to the reductionof the activity of borderline inflammatory cells, as well as the death of microorganisms and intracellular parasites, inhibiting platelet aggregation and improving local blood circulation. At the same timesuperoxide, the product of partial oxygen reduction, accumulates in the focus of inflammation, the amount of which in pathological situations reaches 0.01-0.1 mm. NO and superoxide anion undergo a rapid radical-radical interaction with the formation of peroxynitrite, which isa mediator of oxidative cell damage. In this case, NO easily passes through the outer and inner membranes of cells and, once inside the cell, it damages the DNA of the target cell by deamination, as well as inhibition of ribonucleotide reductase, which regulates the rate of DNA replication. In addition, NO inactivates glyceraldehyde-3-phosphate dehydrogenase, thereby blocking the glycolytic synthesis of ATP, and inhibits electron transport in mitochondria [46]. This explains its cytotoxic effect on the target cell.

Thus, NO, produced by various NOS isoforms, has an extremely important effect on numerous physiological processes in the body. Herewith, the action of iNOS is manifested mainly in pathological situations, therefore, the features of the functioning and regulation mechanisms of this isoform, as well as NO produced by it, depend on the nature of the pathological process and the specifics of the affected organ [47].

NO is capable of triggering a neuron death program due to its unique chemical nature and a large number of targets in a cell; its physiologically active redox forms trigger a damaging attack on the neuron under conditions of ischemia. Numerous studies have proved the direct participation of NO in neuronal destruction in case of the administration of selective inhibitors of neuronal and inducible isoforms of NO synthase (NOS) to animals with acute cerebrovascular impairment (ACVI) and in experiments on animals with a deficiency of the gene encoding the synthesis of inducible NO synthase (iNOS) [48]. There is evidence of an increase in NO concentration in the brain of animals with focal and global ischemia [33]. The concentration of NO increases from the first minutes of ischemia, reaching a maximum in 1-3 days. NOS activity sharply increases in the area of ischemia and penumbra, but it is impossible to define a certain type of enzyme.

At the same time, there is evidence that it is neuronal NOS that forms NO, which causes and complicates damage to neurons, while endothelial NOS improves blood supply in the area of ischemic penumbra. This confirms the role of NO in damage

and death of neurons and indicates the specificity of NOS isoforms. Moreover, the type and stage of stroke should be taken into consideration. It has been proved that in the initial stages of ischemia, the expression of constitutional calcium-dependent NOS, which is due to transmitter autocoidosis, prevails [49]. Nerve cell death, under conditions of overproduction of NO, begins with the mechanisms ofphospholipases activation, overproduction of hydroxyl radical, and modulation of the NMDA receptors. But in the delayed post-ischemic period –since 7-14 days in case of global ischemia and since 1-3 days in case of focal ischemia, NO overproduction is recorded as a result of the activity of inducible NOS activated glia, macrophages and neutrophils [50]. The independence of the inducible form of NOS from calcium enables to maintain high activity of this enzyme for a long time. The expression of this form with hypoxia occurs in 6 hours, in contrast to the constitutional calcium-dependent NOS, which is associated with the later appearance of activated astroglia, macroglia, and inflammatory cells. In the focal form of ischemia, these NO producing cells are located in the penumbra, and in global ischemia, they are located in the structures that are most in need of oxygen. In this regard, the study of the mechanisms of regulation of NOS activity is promising for the development of a treatment strategy for acute cerebrovascular disorders. Scientific literature provides descriptions ofcases with positive results on limiting NOS hyperactivity by the administration of inhibitors and it is indicated that the administration of the latter decreases the progression of brain ischemia [51].

The experiments with the use of various nitric oxide formation modulators on rats with ischemia-reperfusion substantiate the possibility of correcting the adverse effects of the inflammatory process in them by targeted exposure to isoforms of NO synthases, whose role in the implementation of the studied inflammatory reactions at different periods of the reperfusion syndrome is ambiguous. In accordance with the results obtained, the prophylaxis and therapy of the inflammatory process in case of ischemia-reperfusion should be pathogenetically substantiated and include drugs with selective mechanisms for the correction of the L-Arginine-NO pathway [52].

A promising direction is the study of the effectiveness of various inhibitors of NO-synthases in the conditions of experimental cerebral ischemia with respect to limiting the reactions of oxidative and nitrosative stress.

In this research, inhibitors of the three above mentioned isoforms were employed: a non-selective inhibitor of NOS – N-nitro-L-arginine; a highly selective inhibitor of neuronal NOS – N-propyl-L-arginine and a highly selective competitive inhibitor of inducible NOS – (S)-methylthiourea. The experimental animals were divided into 5 groups: I –sham operated animals, II – animals with experimental cerebrovascular impairment (CVI) (control), III –CVI + N-nitro-L-arginine methyl ether (L-NAME) at a dose of 5 mg/kg, IV –CVi + N-propyl-L-arginine hydrochloride (L-PA) at a dose of 2.5 mg/kg; V –CVI + (S) methylthiourea sulfate (S-MT) at a dose of 1 mg/kg [51]. All used compounds are manufactured by Tocris Bioscience (Great Britain). A cerebrovascular impairment was modeled by bilateral occlusion of the common carotid arteries in outbred white rats. The procedure was performed underaethaminalum-natrium anesthesia (40 mg/kg).

Brain tissues located in the area of the sensorimotor zone of the cortex, which were homogenized in liquid nitrogen, were used for biochemical studies. The cytosolic fraction was isolated by differential centrifugation (15,000 g) at a temperature of + 4°C on 0.15 M phosphate buffer pH 7.8. The content of reduced glutathione and its oxidized form was determined fluorimetrically. The activity of enzymes of the antioxidant and thiol disulfide system — superoxide dismutase (SOD), glutathione peroxidase (GPO), glutathione reductase (GR), glutathione S-transferase (GST) was evaluated spectrophotometrically [53]. The intensity of oxidative stress was estimated by the degree of accumulation of products of oxidative modification of proteins – aldehyde and ketone derivatives in the reaction with 2,4-dinitrophenylhydrazine, as well as by the loss of nitrotyrosine, which was determined by enzyme-linked immunosorbent assay using the standard kit “Nitrotyrosine ELISA Kit” (“HyCult biotechnology”, The Netherlands) [21]. The nitrite concentration was determined spectrophotometrically with Griss reagent [54].

The results of the study were processed using the statistical package of the licensed program “STATISTICA® forWindows 6.0”. Statistical processing was performed with the employment of Student’s t-test and Mann-Whitney U-test. For all types of analysis, differences with a level of significance of less than 0.05 (95%) were considered statistically significant [55].

Experimental disturbance of cerebral circulation results in the formation of pathobiochemical reactions of nitrosative and oxidative stress, the signs of which manifested themselves as early as 12 hours after modeling the pathology. The generation of reactive oxygen species and the enhanced formation of nitric oxide in the first 12 hours of the experiment was manifested by an increase in the level of oxidative degradation markers of proteins, a decrease in the content of the reduced form of glutathione with a parallel accumulation of its oxidized form (Table 1). It should be noted that the first reaction of brain tissue to ischemia was an increase in the level of NO andnitrotyrosine,as well as a decrease in reduced glutathione; the values of these indicators reached statistically significant differences ($p \leq 0.05$). The value of the remaining indicators tended to an upward trend. Studying the enzymatic link of the thiol-disulfide system (TDS), a compensatory increase in the activity of indicators was found, which is an adaptive and accommodational reaction of brain tissue to ischemia.

The introduction of NO-synthase inhibitors of different selectivity caused multidirectional changes. For instance, L-NAME, which refers to non-selective inhibitors and provokes an irreversible inhibition of the activity of the constitutional and reversible oneof the inducible isoform of the enzyme, at early stages demonstrates prooxidant properties. The indicated ability of L-NAME to inhibit eNOS disrupts local vasodilation and leads to an aggravation of the overall picture of the pathological process. N-propyl-L-arginine during the first 12 hours of ischemia caused a significant decrease in the level of NO, but the effect on other indicators did not reach statistically significant differences.

L-PA is selective for neuronal NO-synthase, whose activity is significantly increased in the first hours of ischemia. This is explained, firstly, by the observation period –during the period up to 12 hours, nNOShyperactivation caused by calcium ions begins to decrease with a parallel increase in the activity of the inducible isoform, and secondly, inhibition of nNOS leads to the activation of the nuclear factor NF-kB, which induces iNOS [50].

The use of a selective inhibitor of an inducible isoform at the first stage of observation did not significantly affect parameters under study (Table 1). This can be explained by the insignificant contribution of this isoenzyme to the overproduction of NO in this period of time.

Synthesized during the first hours of ischemia, NO interacts with aliphatic and aromatic amines with the formation of N-nitroamines, as evidenced by an increase in the content of nitrotyrosine by 38.6% (Table 1). Further observation showed

an increase in this indicator. So, at the end of the first day, the indicator was 1.7 times higher than the value of the group of sham operated animals; on day 4, the level of nitrotyrosine was 29.6 nmol/g of protein, which is 3.1 times higher than that of the group of sham operated animals. Simultaneously to the formation of nitrosative stress, an antioxidant system malfunction was observed, which manifested itself in the accumulation of free radicals, and as a result, in an increase in the level of products of oxidative modification of protein molecules. An increase of aldehyde and ketone derivative proteins value, relative to the corresponding values demonstrated bysham operated animals, occurred alongside a decrease in the activity of antioxidant enzymes (Tables 1–3). A decrease in the activity of SOD, which plays a key role in the neutralization of the superoxide radical, caused a shift in the TDR towards oxidized intermediate products. At the same time, some of the synthesized NO, binding to the highly toxic superoxide radical, formed a peroxynitrite molecule. In this case, firstly, significant amounts of extremely neurotoxic ONOO- accumulate, and secondly, the bioavailability of NO itself is dramatically reduced.

Table 1. Indicators of oxidative stress and glutathione system in brain tissue 12 hours after the CVI simulation (M±m, n=10)

Indicators	Sham operated animals	CVI	L-NAME	L-PA	S-MT
AFH,cu/gofprotein	1,62±0,15	2,0±0,18	2,35±0,26	1,76±0,14	1,91±0,18
KFH, cu/gofprotein	0,76±0,14	1,04±0,13	1,31±0,2	0,88±0,13	1,06±0,13
NO^-_2, µmol/l	5,47±0,58	7,4±0,43#	6,37±0,8	5,57±0,66	7,22±0,57
Nitrotyrosine, nmol/g of protein	9,63±0,87	13,35±1,59#	15,74±1,3	10,84±1,06	11,33±0,8
SOD cu/(mcgofprotein*min)	272,0±9,98	292,2±9,22	254,1±9,47	280,7±6,43	293,6±5,99
GSH, µ0mol/g of protein	3,95±0,27	3,0±0,22#	2,92±0,23	3,51±0,19	2,97±0,21
GSSG, µmol/g of protein	0,12±0,02	0,19±0,03	0,22±0,03	0,16±0,02	0,18±0,02
GST, mmol/(min*g of protein)	27,56±2,35	31,47±2,48	29,3±2,01	30,42±2,45	29,04±1,95
GR, mmol/(min*g of protein)	13,94±1,53	15,42±0,84	14,9±1,26	15,13±1,63	15,0±1,94
GPx, mmol/(min*g of protein)	69,9±3,4	71,27±2,71	70,51±2,68	70,07±3,0	70,08±1,84

*NBhere and elsewhere: * - p≤0,05 in relation to group of animals with CVA*
*** - p≤0,05 in relation to group of sham operated animals.*

Table 2. Indicators of oxidative stress and glutathione system in brain tissues 24 hours after the CVI simulation(M±m, n = 10)

Indicators	Sham operated animals	CVI	L-NAME	L-PA	S-MT
AFH,cu/gofprotein	1,62±0,15	2,6±0,25**	1,97±0,19*	2,49±0,32	2,28±0,13*
KFH, cu/gofprotein	0,76±0,14	1,39±0,16**	1,03±0,14	1,33±0,14	1,03±0,18
NO^-_2, µmol/l	5,47±0,98	9,1±0,92**	6,04 ±1,03*	8,95±0,87	6,33±0,94*
Nitrotyrosine, nmol/g of protein	9,63±0,87	16,5±1,16**	11,4±1,38*	16,3±1,31	12,4±1,22*
SOD cu/(mcgofprotein*min)	272,0±9,98	234,2±8,55**	261,2±10,2	239,5±8,25	257,6±9,72
GSH, µmol/g of protein	3,95±0,27	1,87±0,13**	2,24±0,26	1,89±0,17	2,27±0,21
GSSG, µmol/g of protein	0,12±0,02	0,29±0,02**	0,21±0,03	0,27±0,03	0,2 ±0,03
GST, mmol/(min*g of protein)	27,56±2,35	20,4±1,83**	21,8±1,87	20,3±1,74	23,6±2,05
GR, mmol/(min*g of protein)	13,94±1,53	10,2±1,08**	12,9±1,33	10,6±1,16	11,7±1,79
GPx, mmol/(min*g of protein)	69,9±3,4	41,9±2,61**	45,2±3,28	42,3±2,73	46,4±3,17

Table 3. Indicators of oxidative stress and glutathione system in brain tissues on the 4th day after the CVI simulation (M±m, n=10)

Indicators	Sham operated animals	CVI	L-NAME	L-PA	S-MT
AFH,cu/gofprotein	1,62±0,15	3,9±0,27#	2,94±0,18*	3,7±0,23	2,46±0,15*
KFH, cu/gofprotein	0,76±0,14	2,2±0,14#	1,89±0,17	2,13±0,25	1,22±0,12*
NO^-_2, µmol/l	5,47±0,98	10,5±0,79#	7,92±0,92	9,26±2,03	6,95±1,04*
Nitrotyrosine, nmol/g of protein	9,63±0,87	29,6±2,06#	17,3±1,84*	25,4±2,15	18,8±1,66*
SOD cu/(mcgofprotein*min)	272,0±9,98	93,4±7,64#	176,4±9,43*	98,3±7,63	179,2±10,1*
GSH, µmol/g of protein	3,95±0,27	0,65±0,11#	1,84±0,36*	0,68±0,13	2,57±0,16*
GSSG, µmol/g of protein	0,12±0,02	0,77±0,14#	0,52±0,09	0,75±0,11	0,49±0,08*
GST, mmol/(min*g of protein)	27,56±2,35	7,6±0,85#	12,9±1,37*	7,5±0,83	17,4±1,57*
GR, mmol/(min*g of protein)	13,94±1,53	6,4±0,59#	8,54±1,44	6,62±0,76	9,98±1,31*
GPx, mmol/(min*g of protein)	69,9±3,4	25,1±2,13#	40,8±3,29*	26,6±2,24	41,3±2,54*

Therapy with an nNOSinhibitor N-propyl-L-arginine on days 1 and 4 did not have a significant effect on the studied parameters, since in more delayed periods the contribution of this isoenzyme to the formation of nitrosative stress is insignificant. Hyperproduction of NO at these stages is caused by the participation of iNOS glial cells, macrophages and neutrophils. The remote nature of iNOS elevation is associated with later activation of astroglia. Unlike nNOS and eNOS, iNOS remains active for a long time and synthesizes significant concentrations of NO. This explains the discovered positive effect of inhibitors that selectively inhibit the activity of an inducible enzyme in the late stages of observation (Tables 2,3). At the end of day 1after the simulation of CVI, the administration of (S) -methylthiourea caused a significant decrease in the manifestations of nitrosative stress, its effect was longer and lasted until the end of the observation. The specified drug on the 4th day of the experiment reduced the level of AFH by 36.9%, and that of KFH– by 44.5%; SOD activity increased by 2.6 times, which was the result of a decrease in nitrotyrosine levels by 53.3%. The use of L-NAME caused generally similar, but less pronounced changes, which is associated with the inhibitory effect of this compound on eNOS activity. A decrease in the activity of the enzymes of the glutathione system, primarily the GPx, which ensures the fermentation of nitrosothiols with the release of NO, is one of the reasons for the decrease in its bioavailabilityunder conditions of oxidative stress.

Thus, the neurotoxic effects of NO depend on the specific isoenzyme of NO-synthase. The analysis of the obtained data indicates the limited role of the neuronal isoform in experimental CVI. The most appropriate target for the pharmacological regulation of NO-dependent mechanisms of neurodegradation is iNOS, since its activity increases 12 hours after the development of ischemia, and the action is carried out over the next few days.

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SUMMARY

NEUROCHEMICAL STATUS OF NITRIC OXIDE IN THE SETTINGS OF THE NORM, ISHEMIC EVENT OF CENTRAL NERVOUS SYSTEM, AND PHARMACOLOGICAL BN INTERVENTION

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The purpose of the given research is to study the efficiency of different inhibitors of NO-synthase in conditions of experimental cerebral ischemia by their capability to limit reactions of oxidative and nitrosative stress.

In the given study a non-selective NOS inhibitor - N-nitro-L-arginine; a highly selective inhibitor of neuronal NOS – N-propyl-L-arginine and a highly selective competitive inhibitor of inducible NOS - (S)-methylurea were used. Cerebral circulation impairment was simulated by means of double-sided occlusion of common carotid arteries. It has been established that neurotoxic NO effect depends on definite enzyme of NO-synthase. Analysis of the obtained data shows a limited role of neuronal isoform in conditions of experimental impairment of blood circulation. The most relevant target for pharmacological regulation of NO-dependent mechanisms of neurodestruction is iNOS because of the fact that its activity begins to increase 12 hours after ischemia development and its action is implemented during several following days.

Keywords: nitric oxide, isoenzymes of NO-synthase, inhibitors, neurodestruction

РЕЗЮМЕ

НЕЙРОХИМИЧЕСКИЕ ПОРТРЕТЫ NO НА ФОНЕ НОРМЫ, ИШЕМИЧЕСКОЙ ПАТОЛОГИИ ЦНС И ФАРМАКОЛОГИЧЕСКОГО ВОЗДЕЙСТВИЯ

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Работа посвящена изучению нейропротективной активности ингибиторов различных изоформ NO-синтазы на модели экспериментального нарушения мозгового кровообращения. Установлено, что на ранних сроках церебральной ишемии разворачиваются реакции окислительного и нитрозативного стресса, опосредованные гиперпродукцией оксида азота. Наиболее уместной мишенью для фармакологической регуляции NO-зависимых механизмов нейродеструкции является индуцибельная NOS, так как ее активность повышается спустя 12 часов после развития ишемии, а действие осуществляется в течение последующих нескольких дней.

Таким образом, нейротоксические эффекты NO зависят от определенного изофермента NO-синтазы. Анализ полученных данных указывает на ограниченную роль нейрональной изоформы в условиях экспериментального нарушения мозгового кровообращения.

რეზიუმე

NO-ს ნეიროქიმიური სურათი ნორმის, ცენტრალური ნერვული სისტემის იშემიური პათოლოგიის და ფარმაკოლოგიური ზემოქმედების ფონზე

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ნაშრომი ეძღვნება NO-სინთაზას სხვადასხვა იზოფორმის ინჰიბიტორების ნეიროპროტექტორული აქტივობის შესწავლას თავის ტვინის სისხლის მიმოქცევის ექსპერიმენტული მოშლის მოდელზე. დადგენილია, რომ ცერებრული იშემიის სხვადასხვა ვადაზე ვითარდება ჟანგვითი და ნიტრატული სტრესის რეაქციები, გაშუალედებული აზოტის ოქსიდის ჰიპერპროდუქციით. ნეიროდესტრუქციის NO-დამოკიდებული მექანიზმების ფარმაკოლოგიური რეგულაციისათვის საუკეთესო სამიზნეს წარმოადგენს ინდუციბელური NOS, რადგანაც მისი აქტივობა იზრდება იშემიის განვითარებიდან 12 საათის შემდეგ, ხოლო მოქმედება გრძელდება მომდევნო რამდენიმე დღის განმავლობაში.

ამრიგად, NO-ს ნეიროტოქსიკური ეფექტები დამოკიდებულია NO-სინთაზას გარკვეულ იზოფერმენტზე. მიღებული შედეგების ანალიზი მიუთითებს ნეირონული იზოფორმის შეზღუდულ როლზე თავის ტვინის სისხლის მიმოქცევის ექსპერიმენტული მოშლის პირობებში.

МОРФОЛОГИЧЕСКИЕ ИЗМЕНЕНИЯ В ПЕЧЕНИ МЫШЕЙ С АНТИФОСФОЛИПИДНЫМ СИНДРОМОМ В УСЛОВИЯХ ПРИМЕНЕНИЯ МОДУЛЯТОРОВ СИНТЕЗА ОКСИДА АЗОТА

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Венозный тромбоз является самым частым проявлением антифосфолипидного синдрома (АФС). Тромбы чаще локализуются в глубоких венах нижних конечностей, нередко в печеночных, портальных, поверхностных и других. У больных АФС выделяют такие формы патологии печени, как обструкция мелких печеночных вен, узловая регенераторная гиперплазия, инфаркт печени (у беременных при HELLP-синдроме или в послеродовом периоде), синдром Бадда–Киари, хронический гепатит, аутоиммунные заболевания [4,9,12,14].

В патогенезе АФС значимую роль играют нарушение коагуляции и повреждение эндотелия сосудов. При эндотелиальной дисфункции нарушается синтез и биодоступность оксида азота (NO) [6,15,16]. В физиологических условиях NO образуется тремя изоформами синтазы оксида азота (NOS), включая эндотелиальную (eNOS), нейрональную (nNOS) и индуцибельную (iNOS). NO, в основном, производится из L-аргинина. После синтеза с участием NOS NO диффундирует в другие ткани или органы. NO не является стабильным соединением, период его полужизни составляет лишь 1-5 секунд *in vivo*. Когда внутриклеточная концентрация кальция повышается, Ca^{2+} попадает в клетки и участвует в синтезе комплекса кальций-кальмодулин, который активирует NOS с последующим превращением L-аргинина в NO и L-цитруллин. Активность iNOS не зависит от концентрации кальция [5,8,10,11,13].

Цель исследования – определение влияния предшественника оксида азота L-аргинина и ингибитора индуцибельной синтазы оксида азота аминогуанидина на морфофункциональные изменения в печени мышей BALB/c с антифосфолипидным синдромом.

Материал и методы. Эксперименты проводились на 50 мышах-самках линии BALB/c (возраст 2-3 мес., вес 25-30 г). Животные содержались в условиях вивария с контролируемым температурным режимом, на стандартном рационе, со свободным доступом к пище и воде. Все манипуляции с мышами проводили в соответствии с положениями «Европейской конвенции по защите позвоночных животных, используемых в экспериментальных и других научных целях» (Страсбург, 1986) и Директивы Европейского Союза 2010/10/63 EU по экспериментам на животных.

АФС моделировали с использованием кардиолипина («Sigma», США), который вводили внутримышечно 4 раза (30 мкг на одну инъекцию, промежутки между инъекциями составляли 14 дней) [2]. Для повышения эффективности иммунного ответа кардиолипин эмульгировали в 75 мкл полного адъюванта Фрейнда (первая инъекция), последующие инъекции проводили с неполным адъювантом Фрейнда. АФС формировался спустя 2 недели после последней инъекции кардиолипина. Подопытных самок мышей разделили на 5 групп (по 10 особей в каждой): I (контроль) – интактные животные; II – животные с экспериментальным АФС, III – животные с АФС, которым вводили блокатор индуцибельной NO-синтазы аминогуанидин («Sigma», США, 10 мг/кг), IV – животные с АФС, которым вводили предшественник NO L-аргинин («Sigma», США, 25 мг/кг), V – животные с АФС, которым вводили L-аргинин в сочетании с аминогуанидином. Для подтверждения развития АФС проводили реакцию микропреципитации с кардиолипиновым антигеном с использованием тест-системы «Антиген кардиолипиновый, для реакции микропреципитации» («Биолек», Украина) [2]. L-аргинин и аминогуанидин вводили внутрибрюшинно один раз в день, в течение 10 дней после формирования АФС. Животные контрольной группы получали внутрибрюшинно идентичные объемы растворителя. Спустя 10 суток с момента подтверждения АФС животных выводили из эксперимента в условиях тиопентал-натриевого наркоза (внутрибрюшинное введение 1% раствора из расчета 50 мг/кг массы животного).

Забор материала для микроскопических исследований проводили согласно методики [1]. Кусочки печени фиксировали в 10% нейтральном растворе формалина, проводили дегидратацию в спиртах возрастающей концентрации, заливали в парафиновые блоки. Изготовленные срезы, толщиной 5-6 мкм, окрашивали гематоксилином и эозином [1]. Гистологические препараты изучали с помощью светооптического микроскопа MIKROmed SEO SCAN (Украина) и фотодокументировали с помощью видеокамеры Vision CCD Camera с системой вывода изображения гистологических препаратов. При изучении морфологической организации печени обращали внимание на изменения паренхимы и основных структурных элементов.

Результаты и их обсуждение. Микроскопические исследования печени экспериментальных животных, которым моделировали антифосфолипидный синдром, установили значительные расстройства сосудистого русла и деструктивно-дегенеративные изменения стромы и паренхимы. Полученные результаты согласуются с данными других авторов [7], которые установили, что поражение печени при АФС сопровождается, в основном, непроходимостью печеночных вен или нижней полой вены, узловой регенераторной гиперплазией, которая ассоциируется с наличием антифосфолипидных антител.

Большинство сосудов полнокровные, особенно центральные и междольковые вены, стенка их истончена и нечетко контурирована (рис. 1).

Для стенки артерий характерны деструкция, утолщение. В большинстве полей зрения наблюдается нарушение дольково-балочной структуры органа. В центролобулярных участках установлены дистрофически измененные гепатоциты с образованием локусов некроза и лизиса, определялись точечные кровоизлияния. Для гепатоцитов характерно уменьшение оксифилии, отек, черты гидропической дистрофии цитоплазмы. Ядра клеток гиперхромные, пикнотически измененные, обнаруживаются темные гепатоциты. Синусоиды визуализировались преимущественно на периферии долек, просветы были полнокровными. В перипортальных зонах обнаруживалась лейкоцитарная инфильтрация (рис. 1).