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TO THE PROBLEMS OF MODELING THE BRAIN ISCHEMIA IN SMALL ANIMALS

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Abstract

In the review article the problems of modeling cerebral ischemia in small mammals are consecrated. The advantages of experimental studies that are based on the similarity of the blood circulation of the brain in humans and animals are indicated. Classification of experimental models for the study of acute and chronic disorders of cerebral circulation, mechanisms of their development and preclinical approbation of new drugs is given. The authors indicate that all experimental models of brain ischemia can be divided into two groups: to study risk factors and pathophysiological studies of brain ischemia. And in the second case, the models of focal and global ischemia are described. In conclusion, the authors point out the difficulties and shortcomings of certain methods of ischemia reproduction, which await researchers to solve the above problems.

Key words: modeling of brain ischemia, small animal

К ПРОБЛЕМАМ МОДЕЛИРОВАНИЯ ИШЕМИИ ГОЛОВНОГО МОЗГА У МЕЛКИХ ЖИВОТНЫХ

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В обзорной статье освещены проблемы моделирования ишемии головного мозга у мелких млекопитающих. Показаны преимущества экспериментальных исследований, основанных на сходстве кровообращения головного мозга у человека и животных. Дана классификация экспериментальных моделей для изучения острых и хронических нарушений мозгового кровообращения, механизмов их развития и доклинической апробации новых лекарственных препаратов. Авторы указывают, что все экспериментальные модели ишемии головного мозга можно разделить на две группы: для изучения факторов риска и патофизиологических исследований ишемии головного мозга. Во втором случае описываются модели очаговой и глобальной ишемии. В заключение авторы указывают на трудности и недостатки некоторых методов воспроизводства ишемии, которые ждут исследователей для решения вышеуказанных проблем.

Ключевые слова: моделирование ишемии головного мозга, мелкое животное

Developed vascularization of the brain of higher vertebrates is an essential element for ensuring the functioning of the central nervous system. The scheme of such a blood supply in mammals implies the presence of four vascular pools. Angioarchitecture - as the order of branching and formation of the main and smaller arteries of the brain, the structure of their walls in rats has similarities with humans, as well as with many other animals.

The vessels contain a pronounced endothelial lining with a developed cytoskeleton and the presence of tight contacts, which is necessary for adequate functioning and interaction of cells [1].

The formation of microcirculation is directly related to neurogenesis as a result of the working interaction of the nerve centers and the vascular capillary environment.

Structural and functional unit of the brain, as in humans is the so-called. module. The vascular network corresponds to the morphology and boundaries of the module and is surrounded by astrocytes, isolating the latter. At the same time, the density and distribution of blood vessels directly depend on the neuronal activity of the brain [2].

On the surface a well-developed basal membrane of cerebral arteries are located circularly located myocytes, then the adventitia is located forming the Virchow-Robin space, which is gradually replaced by astrocytes, which form the pericapillary case for the full operation of the blood-brain barrier. Endotheliocytes and pericytes provide the barrier functions of capillaries, regulate the diameter and movement of blood. Areas devoid of such a barrier, as in humans, contain thin-walled fenestrated capillaries in the area of the hypothalamus, the third and fourth ventricles.

It should be noted that in conditions of circulatory disorders, secondary angiogenesis of cerebral tissue proceeds with the participation of humoral influences, a number of endothelial growth factors, especially fibroblasts, which are formed by glial, and possibly neuronal cells [3,4].

A large variety of small and large animals is used to model vascular pathology of the human brain. At the same time, publications on the comparative structural and topographical correlations, the structure of the arterial circle of the large brain, as well as the morphometry of vascular indicators in the available modern literature are not sufficiently represented. And for an adequate experimental cerebral-vascular damage in animals requires an objective and accurate extrapolation of the available data of this kind to humans.

It is known that in a white rat a closed circle of Willis occurs in 75% of cases. The caliber of each internal carotid artery (ICA) is 1.2 times the diameter of the basilar artery, which adds up to 2.4 times the increase in blood flow. EI Bon, N. E. Maximovich (2018) [2] indicate that the main blood flow to the brain (up to 90%) is carried out by the ICA. In addition, in 50% of animals, the arterial circle of the large brain can appear as "8" as a result of closing the caudal connective vessels with an additional connecting artery. Keep in mind that a high hemoglobin content (16 g / 100 ml) is recorded in a rat [2]. So their inflow to the brain is predominantly via the ICA, which is natural for humans [5].

It should be borne in mind that in the experiment reproducibility of ischemia is not always achieved, this circumstance can be explained by the good development of the arteries of the Willis circle in rats and the severity of collateral blood flow.

Nevertheless, the similarity of the sources of the structure and topography of the vascular system, the main hemodynamic parameters is a good reason to use data from the

simulation of vascular brain pathology in rats with further comparison with the human cerebral vascular pathology (CVP) [6, 7].

At the present stage of development of experimental neurology, a sufficient number of models have been developed, including for the study of acute and chronic vascular dysgemia, risk factors, mechanisms for their development of CVP, preclinical testing of new diagnostic and therapeutic techniques.

Most of the models solve specific problems of studying regeneration processes, the severity of damage to the nervous system, testing various neurotropic, nootropic, vasoactive and other means, as well as treatment strategies with proven effectiveness.

In this regard, the use of small animals is optimal [5-7], which is associated with the previously described features of the structure and functioning of the vascular system, the availability of measurement of basic physiological parameters of life, the size of animals reducing the cost of maintenance and nutrition, as well as high throughput during the experiment . In addition, consideration should be given to the possibility of genetic studies with a large choice of transgenic individuals that broaden the understanding of the specific development mechanisms of specific pathologies. Modern models are also aimed at studying the risk factors for cardiovascular diseases, the number of which exceeds 180, development and their correction, and therefore, prevention and prevention of the effects of brain catastrophes [8-11].

At the same time, an important direction for improving such models is to reduce the traumaticity, material costs, combined with humanity in relation to animals [12].

Currently, the experiment applies and improves complex methods of neuroimaging and functional diagnostics for small animals [13] including study of evoked potentials, encephalographic monitoring, composition of blood gases, blood pressure, etc. Moreover, as with large mammals, these measurements can be performed simultaneously at everyone animal. The convenience of observing sensory and motor behavior and the small size of the brain (for processing speed, biochemical, morphological and other analysis) can also be regarded as the advantage of working with small rodents [13].

Oxygen deficiency is a typical damaging process and the basis of many other pathological changes.

There are hypoxia as a result of insufficient oxygen in the air, its entry into the body, transport to the cells, impairment of utilization. According to the mechanism of occurrence of hypoxic states, the following are distinguished: exogenous; Disturbance of oxygen supply or utilization - respiratory, circular, hemic, histological, mixed. A.Z.Kolchinskaya (1981) [14]

classified hypoxic hypoxia with a decrease in the partial pressure of oxygen, hyperoxic, hypobaric with an increase in the total barometric pressure and hypoxia of the load.

Experimental models of hypoxia imply fixation of animal lifetimes, behavior, and loss of pose. The simplest technique is to place the rat in a hermetic glass jar corresponding to the mass of the animal. There is arterial hypoxemia, a decrease in oxygen consumption in the blood plasma and a decrease in hemoglobin saturation. The introduction of sodium nitrite causes hemic hypoxia with the formation of carboxyhemoglobin. Hypobaric hypoxia is studied in a flow-exhaust pressure chamber with the "rise" of an animal at a speed of 25-50 m / s to a height of 8-11 thousand meters [15].

Priorities remain for researchers in terms of approaching ischemia models to the corresponding clinical task. However, difficulties arise due to the heterogeneity of the etiopathogenetic factors causing ischemic stroke, as well as the clinical variability associated with the continuation, localization, severity of ischemia, and the presence of comorbid systemic diseases. A large block of models examines specific risk factors for ischemia and other disorders directly correlated with stroke, which is an important aspect of the reliability of obtaining results.

Dietary approaches are traditionally used in models of atherosclerosis. Other risk factors that alter the work of endothelial cells with the reaction of vascular wall remodeling are also taken into account [16]. Genetic models of small rodents with the activity of the ApoE gene, other genetic models of hypercholesterolemia (mice with Apolipoprotein B), as well as other transgenic animals are used to study lipid metabolism and accelerated atherosclerosis [17-27].

Histomorphological analysis and the developing pathological process is similar to atherosclerotic damage to human vessels. However, mice do not experience spontaneous thrombotic and embolic total occlusions.

Experimental models of arterial hypertension as the most important risk factor for strokes have been developed. Nabika T. et al. indicate that the advantages of this type of model exclude genetic heterogeneity, environmental interference, statistical uncertainty due to possible small groups of patients. [28]. Wistar rats were obtained with an increased pressure of up to 180-200 mmHg. By the 17th week of life, at the same time, despite the clinic, serious problems in the form of ischemic stroke (IS) rarely develop. Animals with the activity of genes involved in vasoreactivity that alter NO function with a reliable development of IS for 9–13 months have been derived [29,30].

Not always the exact mechanism of the development of arterial hypertension is clear even in the presence of a known gene in transgenic rats. Experimental models of an important factor of an atherothrombosis strengthening - a hyperhomocysteinemia are used. The concentration of plasma homocysteine can be increased tenfold. This can be achieved by disrupting the CBS gene, cystathionine beta-synthase, as well as in mice with a deficiency of a specific oxidooctase encoded by the gene [31].

To study the mechanisms of aging as the main factor in the development of AI, mice of the OXYS line associated with a genetic increase in sensitivity to oxidative stress were bred. Transgenic mice are used as a model of CADASIL small vessel disease.

Oxidative stress is a universal pathophysiological process that occurs during ischemic damage to the central nervous system [34]. Experimental models of IS are known using indicators of metabolism in free-radical lipid oxidation (LPO) [32]. In rats, the maximum number of active metabolites of was determined in the first hours of the experiment [33-35]. In another series of experiments aimed at reperfusion of the brain after vascular ischemia, there is an even greater risk of re-oxygenation of neurons with an "explosion" of the synthesis of reactive oxygen species, with the development of oxidative stress [32,36].

The literature data confirm the leading role of the intensification of lipid peroxidation processes in the development of neurodegenerative states [37–39].

Toxicity, induced hyperactivation of the neurotransmitter system of excitatory amino acids, damage to cell membranes and mitochondria, intensification of lipid peroxidation processes, hypersecretion of proinflammatory cytokines and growth factors, inflammation, apoptosis are often considered as potential targets for the development of therapeutic effect [33].

An important area of experimental models of cerebral ischemia is the study of impaired functioning of neurotransmission. In this case, the main role is assigned to glutamate, the release of which leads to "death from arousal" [40-43]. A closed pathological circle is formed, in which a cascade of interconnected pathological reactions with ischemic neuronal damage, increased production of excitatory neurotransmitters, a deficiency of high energy substances, accumulation of free calcium, nitric oxide, proinflammatory cytokines, endogenous cannabinoids and other substances increased severity of lipid peroxidation processes [44].

From the above it follows that the experimental models can be divided into two groups:

1. Models of studying risk factors for ischemic neurons that provoke damage to cerebral vessels, as well as preventive correction.

2. Models of pathophysiological study of chronic cerebral ischemia, AI, transient ischemic attacks, as well as for testing the therapeutic possibilities of drugs (neuroprotection, neuroplasticity, regeneration, recanalization, etc.).

In turn, the second point of the consequences of acute and chronic ischemia is further divided into two blocks of models:

a) focal (focal, regional) ischemia "as a stroke";

b) global ischemia of the "cardiac arrest" type.

To create models of focal ischemia in rodents, occlusions are used in the form of arterial ligation:

The method of Pulsinelli W. A. models temporal ischemia by ligation of the common carotid arteries (CCA) and the external carotid artery with additional ligation of the vertebral artery (VA) [45].

Method Koizumi J. - by ligation of the right common carotid and external carotid arteries, followed by the introduction of the occluder through bifurcation of the CCA into the internal carotid to the middle cerebral artery and fixation of the occluder by ligation of the ICA [46].

Sufianov G.Z. Method et al. uses carotid occlusion - ligation of the common and external carotid artery and the introduction of the occluder through the common carotid artery and then into the ICA and ligated the OCA of the opposite side [47].

The method of Pulsinelli W. A. [45] modified by Mitsuo Yamaguchi et al. [48] consists in a one-step anterior approach with four vessels occlusion (4VO).

Tamura et al. (1981) suggested occlusion of the MCA in the proximal segment using subtemporal craniotomy [49-51].

In addition to ligation of the arteries is used:

Thermo-, electrocoagulation in order to burn through the middle cerebral artery (MCA) [52].

Endothelin-1-induced narrowing of the arteries. A method for the combined use of endothelin and occlusion of CCA has been developed.

Introduction of microfilaments leaving or in a temporary interval removing suture material, causing reperfusion.

The use of a thread in the vessel lumen in the form of a 4-0 nylon suture insert, and then selecting the thickness of the thread blocking the vessel lumen [53-55].

Modeling of the occlusion using the CCA filament according to the J. Koidzumi method with doppler examination allows to control the degree and stability of the occlusion and exclude animals with atypical cerebral blood flow from the experiment.

Vascular embolization with synthetic macrospheres induces large foci of ischemia, microspheres up to 50 microns - multifocal infarctions. [56].

Occlusion of the VSA with autologous blood clot is used to study thrombolytic and reperfusion therapy.

For photoinduced vascular thrombosis, IV injection of the photosensitizer is performed. And for irradiation using an argon laser or visible light. Water-soluble xanthene dyes are used as a photosensitizer, including rose bengal with an induction λ of 560 nm. [36].

In modern models of cerebral ischemia, an introduction to various vessels is also used: cobra venom; human atherosclerotic masses from the aorta; platelet aggregates (a mixture of platelets and white blood cells); and laser coagulation of the arteries [36].

In models of **global ischemia**, the CNS uses a complete and incomplete arrest of blood circulation in the brain.

Intracardiac administration of an aqueous solution of potassium chloride is used as a complete ischemia, which inhibits the contractility and myocardial excitability [57];

Decapitation to study the mechanisms of the work of fast-acting drugs, biochemical studies [60];

Placing a harness (cervical turnstile) or cuff on the neck [58-59], the technique is effective for studying pathological processes in the hippocampus and trunk [60];

Compression of the chest of the animal based on the method of modeling clinical death - Patent of Ukraine No. 28969. Then, cardiopulmonary resuscitation was carried out [61,62];

Simulation of heart failure by retrosternal clipping of vessels over the heart. Complete ligation / compression of all arteries extending from the heart [63].

Induction of ventricular fibrillation to simulate cardiac arrest;

Lowering blood pressure (bloodletting) or exsanguination of the animal, followed by recovery;

Ligation of the common carotid and subclavian arteries distal to the discharge of the internal thoracic arteries and proximal to the separation of the VA according to the Rozvadovsky method [64];

M.P. Plotnikov et al. (2015) [65] used two surgical access to the left CCA, the brachiocephalic stem and the left subclavian artery. The operation was carried out bypassing the pleural cavity to exclude complications, pneumothorax.

Among small rodents in terms of developing a model of ischemic brain damage, there is a gerbil, which in vascular anatomy has no connections between the main brain basins (carotid and vertebrobasilar). Global ischemia can be caused by bilateral occlusion of the carotid artery. At the same time, technical implementation is much easier than in rats [56]. Unilateral occlusion of the carotid artery also causes damage in the form of unilateral infarction with severe neurological symptoms in 30-40% of cases.

Models of **incomplete global ischemia** are intermediate between focal and global ischemia. These include:

"Model by Rice" or "Rice-Vannucci" hypoxic ischemia by permanent occlusion of one CCA and subsequent placement into the atmosphere with low (no more than 8%) oxygen content. A variant is the bilateral occlusion of two CCA. Occlusion of two or only the right CCA, followed by a decrease in atmospheric pressure in the pressure chamber to 277 mm Hg. Art. with an exposure of 90 minutes, it allows to study hypoxic hypoxia [56].

Variant of two-vascular occlusion of CCA and hypotension (including controlled drug hypotension or bleeding) Onken M. et al., 2012. In these experiments elements of hypoxia and ischemia are combined.

The bilateral occlusion of two CCA by the method of Eklof and Siesjo (1972) is widely used to study the energy state of the brain after incomplete ischemia (Smith et al., 1984) [66].

In conclusion, it should be noted that among the diversity of experimental models that solve the problem of studying the vascular pathology of the brain there are certain difficulties. Low reproducibility of ischemic damage to the central nervous system, due to the anatomical difference in the structure of the arterial circle of the large brain - in half of the cases there is an additional connective artery and pronounced collateral blood flow.

Inaccuracy of ischemia reproduction in a specific region of the brain with a number of focal models of cerebral circulation disorders.

The complexity of surgical access to certain arteries of the respective basin implies the need for special skills from the researcher. Aggressiveness of the so-called. "phased" methods of occlusion of several arteries, which is significantly different from the actual conditions for the development of stroke.

The use of various occluders contributes to trauma, perforation of the vessel with possible postoperative complications. The need for special equipment, optical instruments, a microscope, microsurgical equipment, laser or photo-optical installations, a pressure chamber, a thermocoagulator, microfilaments with various coatings on the intravascular part, devices for inducing ventricular fibrillation, etc.

The variety of anesthetic methods and tools and their combinations can also negatively affect the data obtained. The same circumstances apply to complex diagnostic equipment of various modifications for the study of evoked potentials, brain bioelectrogenesis, blood circulation velocity, vascular resistance, modern neuroimaging methods, etc. As well as the use of special laboratory equipment and reagents, which makes it difficult to compare and interpret data when using various technical devices.

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