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Modern Aspects of the Pathogenesis AND the Models of Ischemic Stroke

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Abstract: The incidence of ischemic stroke remains high in many countries, despite a declining trend in the incidence of brain circulation disorders. Limited knowledge of the pathogenesis, diagnosis, clinical presentation, and treatment of this life-threatening disease can be complemented by modelling of ischemic stroke on animals, particularly, in rodents.

Keywords: ischemic stroke; pathogenesis of ischemic stroke; occlusion; middle cerebral artery; embolic stroke; phototrombosis.

High incidence and the detrimental effects of ischemic stroke are due to a lack of knowledge of the pathogenesis, diagnosis, clinic and treatment of this life-threatening disease. Some issues of pathogenesis can be clarified by modeling ischemic stroke in animals, in particular, rodents (rats, mice) [4]. In this respect, improvement of the ischemic stroke modeling, implementation of animal maintenance and care recommendations, optimization of surgical techniques and anesthesia, and pain minimization will contribute to obtaining more accurate results of scientific research [1]. The importance of solving of these problems has been confirmed by the expert meeting organized by the the National Centre for the Replacement, Refinement and Reduction of Animals in Researchto assess existing methods for ischemic stroke modelling, discuss proper animal care and develop relevant recommendations [3].

Simulation of cerebrovascular accidents in the middle cerebral artery territory has been the most preferred model so far. Variants of this method allow obtaining a cortical infarct using the occlusion of more distal parts of the middle cerebral artery [11–14]. When choosing an occluder, its diameter and flexibility as well as its tip coverage are essential. The occluder flexibility minimizes the risk of artery damage (puncture) in the area of the skull base. A long, larger diameter occluder provides more reliable occlusion, but can also block other vessels coming directly from the circle of Willis to the sub cortical structures. Beyond the middle cerebral artery, the thalamus, hypothalamus, and hippocampus may be in the area of impaired circulation due to occlusion of proximal arteries arising from the middle cerebral artery (e.g. the anterior chorioidal and hypothalamic arteries). Some animals may have a congenital incomplete circle of Willis. Small diameter occluders are used more often, restricting ischemic lesion to the blood supply area of the middle cerebral artery. More variable results are observed on models with temporal occlusion of the middle cerebral artery compared to its permanent occlusion. This is due to the development of reperfusion damage resulting from partial recovery of blood flow. Various factors such as gender and age of anumals, previous stress, and environment may have a significant impact on the study results, especially on mortality and recovery timeframe [4,5].

Many issues of the pathogenesis of embolic strokes remain poorly studied [8, 11]. In this regard, methods of experimental embolic stroke reproduction are under development, in particular the method using a thin cannula containing a blood clot. This model is the most complicated

technically and also in terms of obtaining reproducible results. The use of this model results in high mortality of experimental animals (over 30%).

Stroke may also be caused by thrombin injection into the lumen of the distal branch of the middle cerebral artery [12, 13]. The possibility of spontaneous thrombolysis, affecting the variability of the results, should be taken into account. This model can be used to study thrombolytic drugs, for example, rtPA. The size of brain infarcts with this model is small, thus, neurological signs are minimal or absent.

In some cases, permanent occlusion of the main trunk of the middle cerebral artery is performed by electrocoagulation [6]. Craniotomy is performed and the brain dura mater is dissected. Electric current is delivered through the artery by means of thin diathermic pincers. This leads to blood coagulation, arterial wall damage, cerebral ischemia distal to the electrocoagulation site. At the same time, there are new modifications of acute cerebrovascular accident modeling, allowing for a detailed elaboration of their pathogenesis and preclinical testing of new methods of ischemic stroke treatment. Animal Maintenance Before and After Stroke The rules for handling the experimental animals are specified by the European Parliament [10]. The duration of animal acclimatization should be at least 7 days before the experiment. Animals should be inspected daily to assess their appearance and control their body weight. Irregular internal animal transportation may affect their physiological parameters causing sleep disturbances, increased plasma corticosterone, low immunity, and reduced body weight [9]. It takes from 2 to 4 days for these parameters to return to normal levels. Normalization of food consumption and sexual behavior after transportation requires more than 4 days. Transcontinental transportation of animals leads to longer circadian rhythm disorders, and their resynchronization takes more than 2 weeks. When preparing the animals for the experiment, it is important to ensure the stability of daily exposures in order to maximally avoid side effects. Animals live in hierarchies where there is domination and subordination. Relocation of animals to other groups provokes stressful situations, disrupts social relations and causes aggression [7]. The same researcher should also work with animals during acclimatization.

General anesthesia leads to a lack of blink, so the eyes must be protected with a gel or liquid, which prevents the corneal drying during anesthesia. Body temperature must be monitored as hypoor hyperthermia may develop. Brain cooling (therapeutic hypothermia) has effective neuroprotective properties in modeling ischemic stroke [14].

Blood oxygenation can be controlled invasively by performing arterial blood gas analysis (using PaO2, mmHg) or non-invasively by pulse oximetry (SpO2, %). The impact of anesthetics on respiratory and circulatory functions depends on the dose, therefore the use of lower doses of anesthetics is important. Monitoring of the basic physiological parameters during anesthesia is necessary to ensure its stability, increase the study reproducibility, reduce mortality and complications in the postoperative period. Non-invasive monitoring methods should also be used to assure physiological stability. In particular, pulse oximetry allows assessing cardiorespiratory functions. Capnography is recommended to standardize respiratory function assessment in stroke modeling and in fMRI studies, where PaCO2 stability is crucial. To compensate for fluid loss, a saline or Hartmann solution should be administered. Solutions should be given every 1–2 hours during anesthesia [17-19].

In recent years, emphasis has been placed on the study of drugs and methods that possess neuroprotective properties in the experiment in animals and in patients with ischemic stroke. In particular, these properties exist in the vascular endothelial growth factor, cerebral miRNA, electroacupuncture, adropin, glia, nicotinamidadeninucleotide phosphate, dimethylfumarate, hypothermia, and steroid hormones. Neuroprotectors enhance resistance of central nervous system structures to oxygen starvation. Anesthetics also have these properties, and their use has led to significant success in developing experimental models of human stroke. Medical gas xenon has a neuroprotective effect [15]. Exceptional properties of xenon make it different from other neuroprotective agents, so it plays a special therapeutic role in stroke, both independently

and in combination with other treatments. The neuroprotective effect of xenon can be mediated by N-methyl-d-aspartate receptor inhibition [16]. Neuroprotective effects of xenon delivered by xenon-containing echogenic liposomes through controlled ultrasound release in early brain damage after subarachnoid hemorrhage have been evaluated. Ultrasound imaging and electron microscopy have shown that liposomes containing xenon have a unique structure that allows its two-stage release. The use of xenon effectively inhibited bleeding, improved overall neurological function and reduced damage to motor function along with apoptotic neuronal death, as well as decreased mortality [7]. Neuroprotective effects were already shown in the blood xenon level of less than 20% of the estimated neuroprotective concentration [5]. Binding to the active center of several serine proteases is one of the unique properties of xenon. Since the active site of serine proteases is structurally conservative, xenon's ability to alter the catalytic activity of a serine protease plasminogen tissue activator (tPA) has been investigated. Molecular modelling and in vitro and in vivo studies have shown that: 1) xenon is a tPA inhibitor; 2) xenon inhibits tPA-induced thrombolysis; 3) in the post ischemic period, xenon inhibits ischemic brain damage, tPA-induced brain haemorrhage, and blood-brain barrier damage [15]. At the same time, stroke outcomes may be affected by the pharmacological effects of anesthetics on nervous function, their species-specific, medical and dose-specific effects on cerebral blood flow and metabolism, autoregulation, ischemic depolarization, excitotoxicity.

Conclusion

Thus, there are several experimental ischemic stroke models. The most adequate stroke model is the one using the blood flow occlusion in the middle cerebral artery territory. Two variants of this method allow obtaining massive brain infarcts (blood flow occlusion with subsequent reperfusion) and small infarcts (without blood flow restoration). This corresponds to different variants of ischemic stroke in humans.

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