COMPARATIVE ANALYSIS OF THE DEGREE OF ISCHEMIC BRAIN DAMAGE IN EXPERIMENTAL RIGHT OR LEFT COMMON CAROTID ARTERY OCCLUSION IN VIVO

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Abstract. The features of ischemic brain injury outcome in C57BL/6 mice depending on the right or left common carotid artery occlusion are characterized. The right-hemispheric focal ischemia decreases the body weight, causes spatial memory impairment, and activates the development of a pronounced long-term neurological deficit characterized by ipsilateral limb paralysis, ptosis and muscle dystrophy, which is accompanied by perivascular brain tissue edema. In the left-hemispheric focal ischemia, the neurological status impairments are also observed, but they less pronounced than in case of right-hemispheric ischemia. Moreover, preference to study novelty is reduced, and long-term emotional strain is revealed. The peculiarity of ischemic injury using the left common carotid artery occlusion is accompanied by the presence of hemorrhages and dilated capillaries in the damaged brain hemisphere.

Keywords: brain ischemia, hemispheric ischemia, right common carotid artery occlusion, left common carotid artery occlusion, mice, neurological deficit, behavior, memory.

List of abbreviations

CNS – central nervous system;

DC – discrimination coefficient.

Introduction

For many years, ischemic brain diseases remain one of the most acute problems for global public health (Donkor, 2018). According to statistics, over the past 15-20 years, the number of strokes diagnosed worldwide has increased annually; at the same time, the number of lethal outcomes has also increased (Katan & Luft, 2018). This is primarily linked to demographic transition resulting from the increased life expectancy of the population and the sharp increase in the proportion of elderly and senile people who present the prevailing part of the risk group (Gorelick, 2019). Approximately 6 million people suffer from cerebral stroke, and the mortality rate reaches 4.7 million people every year worldwide. In most countries, including the Russian Federation, ischemic stroke ranks second in the structure of total mortality, and in a number of regions it has become a leader, displacing the mortality values of myocardial infarction (Machinsky et al., 2019).

Ischemic brain diseases are also a major cause of disability in the population. The main effects of ischemic stroke are severe neurological impairments, including motor, memory and learning disabilities (Ojaghihaghighi et al., 2017; Tadi & Lui, 2020).

Thus, the problem of ischemic brain damage has both an undeniable social importance and an essential aspect for understanding the fundamental patterns of nerve cells functioning during stress.

In the pathophysiological aspect, ischemia is a peripheral circulation disorder based on the restriction or complete cessation of arterial blood flow due to narrowing or blockage of the leading arteries. Among the variety of mechanisms participated in brain ischemia development, the key point is an acute deficit of oxygen and glucose supply and the oppression of energy production processes (Kirkman & Smith, 2016).

Special attention is now focused on studying the peculiarities of CNS functioning and the degree of neurological severity, depending on the location of ischemic lesion source (McCluskey et al., 2016; Portegies et al., 2015). A number of clinical studies have shown that left-hemispheric brain damage has a more pronounced neurological deficit, with an increased incidence of lethal outcomes (Hedna et al., 2013; Li et al., 2019). Key consequences of left hemispheric stroke are right-sided weakness/paralysis, sensory impairments, aphasia, disorders in speech, vision, and memory, impaired ability to read, write, perform mathematical calculations, and analyze and systematize the obtained information. Moreover, patients with left hemispheric lesions have more pronounced violations of higher mental functions and more susceptible to depression (Vein et al., 2007; Walter, 1995).

Ischemic brain lesion in the right cerebral hemisphere leads to the development of left-sided weakness/paralysis, sensory, visual, and memory impairments, spatial perception (depth, directions etc.) disorders although the fluency of speech is preserved (Hedna et al., 2013). Sensitivity disorders, anosognosia, half-attention syndrome, mental disorders and depression are predominated (Shimoda & Robinson, 1998).

However, there is a methodological impossibility to study the mechanisms of cerebrovascular pathology development in humans and, therefore, a necessity to use experimental animal models (Canazza et al., 2014). Nowadays, a wide range of in vivo ischemia models has been developed to solve specific tasks, including studies of the degree of CNS damage in acute and chronic ischemic conditions, adaptive and regenerative mechanisms, the determination of risk factors, testing of neurotropic, nootropic, vasoactive drugs of a new generation, and development of diagnostic methods and approaches for effective therapeutic correction (Vasil'ev et al., 2015; Kaya et al., 2017; Kumar et al., 2016).

Occlusion of main brain vessels is the most common method which allows simulation of both focal and global brain ischemic lesions. Recent studies have shown that depending on right or left middle cerebral artery occlusion, the ischemic damage outcome in rats is different. Sensomotor disturbances prevailed in the left middle cerebral artery occlusion, whereas cognitive disturbances prevailed in the right-hemispheric ischemic injury (Zhai & Feng, 2018). Other studies have been demonstrated that the middle cerebral artery occlusion of left and right hemispheres leads to sensomotor deficit and increases anxiety levels in animals (Hedna et al., 2013). In the case of posterior cerebral artery occlusion, mnemonic and learning disabilities are provoked (Livingston-Thomas et al., 2015).

Previously, we developed a model of global ischemia with modification for mice by using irreversible bilateral occlusion of common carotid arteries. The high percent of mortality, the pronounced changes in neurological status and mnemonic functions are revealed. Moreover, we described the individual characteristics of different murine lines according to the degree of resistance to simulated stress (Mitroshina et al., 2017). Based on this model, we decided to characterize the degree of CNS damage and peculiarities of mnemonic and behavioral disorders in mice with focal left- or right-hemispheric ischemia.

Thus, the goal of this study was to determine the features of ischemic brain damage in experimental right or left common carotid artery occlusion in C57BL/6 mice.

Methods

Ethics statement. The experiments were carried out on female C57BL/6 mice (7-8 weeks old) weighing 20.9-22.6 g. All experimental procedures were performed in accordance with the Rules for the Work using Experimental Animals (Russia, 2010), International Guiding Principles for Biomedical Research Involving Animals (CIOMS and ICLAS, 2012), as well as the ethic principles established by European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Strasbourg, 2006) and approved by the Bioethics Committee of National Research Lobachevsky State University of Nizhny Novgorod.

The animals were divided into the following group: 1) intact animals; 2) sham-operated animals undergoing tissues incision and searching of arteries without their occlusion; 3) left-hemispheric ischemia – the animals with left common carotid artery occlusion; 4) right-hemispheric ischemia – the animals with right common carotid artery occlusion.

Brain ischemia model. A model of irreversible unilateral occlusion of the common carotid artery is used. Before surgical procedures, each animal was anesthetized with an intraperitoneal injection of Zoletil 100 (Virbac Sante Animale, France) in the dose of 70 mg/kg. In the absence of pain reflex (limb tweezing response), wool was removed from the front surface of the animal's neck, and a soft tissue incision was carried out. In the operating field, the left or right common carotid artery was isolated, and the vessel was ligated with non-absorbable ligature threads (Fig. 1). The wound was then sutured and powdered by Streptocide in order to prevent infection. The duration of one surgery was not more than 10–15 minutes on average.

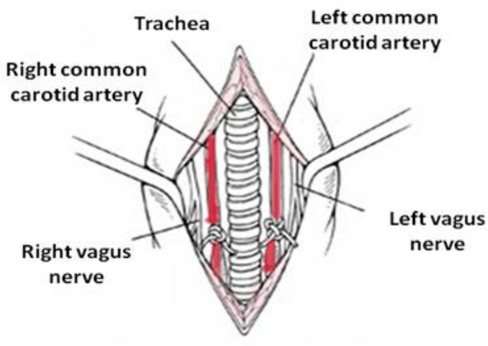

Fig. 1. Schematic representation of the location of target arteries for ischemic brain injury modeling (modified according to http://jim.hutchins.name/research_skills.html)

In the post-ischemic period, the animals were assessed for weight characteristics, neurological status, behavioral and locomotor activity, and spatial memory state.

Neurological status determination. Functional state of the nervous system of experimental mice in the post-ischemic period was assessed according to Neurological impairment assessment in small laboratory animals (Kul'chikov et al., 2008). Each animal was tested by 10 involuntary congenital behavioral reactions, and each response was evaluated by a scoring system, where 2 points meant a lack of reaction. The obtained values were summarized and interpreted as follows:

from 10 to 20 points – severe CNS damage;
from 6 to 9 points – moderate CNS damage;
from 1 to 5 points – light CNS damage.

Hanging wire test. To assess the degree of locomotor activity lesion, gripping reflex and anterior limb strength of experimental animals were measured using Hanging Wire test according to Hoffman & Winder, 2016 with a modification.

The animals were placed on a wire 1 m long, 2.5 mm in diameter, located at the height of 50 cm above the floor during 1 min. The test was repeated three times, and then the average time spent by the animal on the wire was calculated.

Open field test. The general locomotor and orienting-exploratory activity of the experimental animals were tested in the "Open field" setup (LE800S; Panlab Harvard Apparatus, Spain) in the early and late post-ischemic period. Five-minute registration of animal behavioral response was performed by using a Sony SSC-G118 (Japan) camera. The following behavioral reactions were analyzed: vertical motor activity (the number of upright postures), emotional state (the number of grooming acts, acts of defecations and urinations, and the residence time in the arena center).

Novel object recognition test. The spatial memory state in mice was evaluated using the novel object recognition test based on memory retention of familiar objects and a natural rodent preference for novelty (Dere et al., 2007). Plastic balls A (red), B (purple), B (yellow) with a diameter of 6 cm were used as the objects of recognition.

The test was conducted in several stages:

1. Acquaintance. On the day of surgery, the animal was placed in a round arena (90 cm in diameter) for 3 min for free movement in order to study the environment where it enters for the first time. Then the animal was taken out of the arena and was outside for 3 min, after which it returned to the investigated space, where objects A and B were previously placed. The time for studying the objects was 3 min.

2. Learning. The next day after surgery, the animal was placed in the arena with objects A and B for free movement for 3 min.

3. Testing. 24 hours after the "Learning" stage, the animal was placed in the arena with

objects for free movement for 3 min. Object A was previously changed to object C.

Discrimination coefficient served as a criterion for objects preference which was calculated according to the following formula:

$$DC = t (C) - t (B) / t (C) + t (B),$$

where DC – discrimination coefficient; t(B) – overall time spent around object B (old object); t(C) – overall time spent around object B (novel object); DC values more than 0.1 means that the animal distinguishes between new and old objects.

To determine the state of spatial memory, an additional test was carried out. For this, we used old objects A and B; however, object B was relocated during the test.

Morphological assessment

Histological studies were performed on day 60 after ischemia modeling. The brains of experimental animals were surgically removed and then fixed in 10% formalin solution at room temperature during the day. After the incubation period, the brain was placed in 15% (24 hours) and then in 30% (the next 24 hours) of sucrose solution at room temperature. Next, the samples were transferred on a platform of a Leica CM1520 freezing sliding cryostat (Leica, Germany) and gradually filling with cryogel (Leica, Germany).

The brain was cut into 10 μm thin corona slices. Every fifth slice of each sample was placed on a slide and dried in the air within 24 h. The obtained slices were then stained according to a standard hematoxylin-eosin method (PanReac AppliChem, Germany). Next, the slices were dehydrated in alcohols of upward concentration, purified in xylols and embedded in a mounting medium (Thermo Fisher Scientific, USA).

The samples were examined using a Zeiss Primo Star light microscope (Zeiss, Germany) with integrated an Axio CamMRc camera (Zeiss, Germany).

Statistical analysis

The obtained data are presented as a mean ± a standard error of the mean (M±SEM). The significance of differences between the experimental groups was determined using Sigma Plot 11.0 software (Systat Software Inc., USA) and ANOVA test. Differences were considered significant at $p < 0.05$.

Results

Early effects of ischemic brain injury. Analysis of weight characteristics revealed a significant decrease in body weight of animals subjected to common carotid artery occlusion on the first day after surgery (Table 1). At the more distant post-ischemic period, the animals from the "Left-hemispheric ischemia" group continued to show a tendency to weight loss relative to the "Intact" group. On day 14 after ischemia modeling, an average weight of animals in the "Right-hemispheric ischemia" group was significantly lower than the values registered before surgery and the "Intact" group and amounted to 20.7±0.6 g.

Analysis of behavioral reactions in the "Open field" test did not reveal significant changes in the emotional state and orienting-exploratory activity of the experimental mice (Table 2). However, on the first day after ischemia modeling, there was a tendency to decrease vertical motor activity in the "Left-hemispheric ischemia" and "Right-hemispheric ischemia" groups that suggests the presence of motor function impairments.

To confirm this statement, the animals were assessed for neurological status and examined for muscle strength in the Hanging wire test (Table 3). It was shown that the animals with common carotid artery occlusion show evidence of CNS damage. According to Neurological impairment assessment, these changes were mainly related to the development of anterior limb paralysis (ipsilateral in 75% of cases, contralateral in 25%) and ptosis. The most pronounced manifestations of the neurological deficit are observed in animals with right carotid artery occlusion, in particular during the first seven days of the post-ischemic period (day 1 after surgery: 3.5±0.5; day 7 after surgery: 4±0.1).

Table 1

Weight characteristics of mice in the early post-ischemic period

Experimental groups	Before surgery	Post-ischemic period, day		
		1	7	14
Intact	22.9±0.3	22.7±0.3	22.3±0.5	22.6±0.2
Sham-operated	22.4±0.7	19.8±1.1	20.0±2,2	21.6±0.5
Left-hemispheric ischemia	21.5±0.3	19.8±0.5*#	20.7±0.6	21.4±1.3
Right-hemispheric ischemia	21.4±0.2	19.7±0.5*#	20.3±0.9	20.7±0.6*#

The data are presented in grams
* – versus "Intact", # – versus "Before surgery", $p < 0.05$, ANOVA

Table 2

Parameters of behavioral reactions of mice on the «Open field» tests in the early post-ischemic period

Experimental groups	Number of upright postures			Acts of grooming			Acts of defecation		
	Post-ischemic period, day								
	1	7	14	1	7	14	1	7	14
Intact	22.0±8.7	8.7±3.2	3.7±0.9	4.8±1.8	2.3±0.7	1.7±0.3	1.3±0.9	1.3±0.3	1.7±0,3
Sham-operated	28.0±4.9	7.3±1.9	9.3±3.2	7.3±3.2	1.3±0.3	0.7±0.3	0.3±0.3	2.3±1.5	0.7±0.3
Left-hemispheric ischemia	11.7±4.8	11.1±4.2	5.1±1.8	3.0±1.6	2.0±0.9	3.0±1.0	0.4±0.3	1.4±0.7	1.6±0.7
Right-hemispheric ischemia	8.3±2.7	5.8±3.1	6.3±1.7	0.8±0.3	0.8±0.5	1.3±0.6	0.8±0.5	0.8±0.5	0.3±0.2

* – versus "Intact", $p < 0.05$, ANOVA

Table 3

Neurological status of mice in the early post-ischemic period

Experimental groups	Neurological status (points)			Average time spent on the wire, s		
	Post-ischemic period, day					
	1	7	14	1	7	14
Intact	0	0	0	22.0±2.6	20.0±7.0	11.0±3.6
Sham-operated	0	0	0	20.0±7.1#	16.0±5.0#	18.7±7.0#
Left-hemispheric ischemia	1.3±0.4*	1.6±0.4*	1.0±0.3*	0.6±0.4*#	3.1±1.9*#	7.4±3.0*#
Right-hemispheric ischemia	3.5±0.5*	4±0.1*	2.3±0.7*	0*	0*	1.2±0.4*

* – versus "Intact", # – versus "Right-hemispheric ischemia", $p < 0.05$, ANOVA

In addition, during the Hanging wire test the animals from the "Right-hemispheric ischemia" group showed pronounced muscle weakness of anterior limbs. During the first seven days after ischemic injury, the animals of this experimental group could not hold on the wire and spent the shortest time on it on day 14 of the post-ischemic period. Dystrophy of the anterior limbs was also observed in animals with left common carotid occlusion, but the retention time on the wire was significantly higher than that of the "Right-hemispheric ischemia" group.

Spatial memory assessment in the Novel object recognition test revealed that the mice withthe right and left common carotid artery occlusion significantly reduce the preference for novelty research (Table 4). The animals of the “Left-hemispheric ischemia” and “Right-hemispheric ischemia” groups spent the least time with a new or relocated object. The smallest discrimination coefficient for new object recognition was in the “Left-hemispheric ischemia” group (0.2±0.05); the negative discrimination coefficient was calculated in the “Right-hemispheric ischemia” group during the test with the relocated object (–0.1±0.05).

Remote effects of ischemic brain injury. The animals were re-tested in the “Open field” on day 60 after ischemia modeling (Table 5). It was shown that the mice with left common carotid artery occlusion were experienced a latent level of emotional tension. The animals from the “Left-hemispheric ischemia” group spent in the arena center the longest time (96.7±32.6 s) which exceeded in 3 times the values of the “Intact” group (33±8.4 s). The number of acts of grooming, defecation and urination was comparable with those of the “Intact” group.

On the other hand, the mice with the right common carotid artery occlusion were on the periphery of the arena prevailing part of the time. The time spending on the arena center amounted to 4.7±1.1 s. However, this group of animals had benefits of passive fear, characterized by the increased acts of grooming (Intact: 7.0±3.5; Right-hemispheric ischemia 17.0±5.2).

Neurological deficit assessment showed that both left and right common carotid artery occlusion leads to impairments in motor and reflexive activity in animals in the remote post-ischemic period. The neurological status in animals of the “Left-hemispheric ischemia” and “Right-hemispheric ischemia” groups was 6±0.5 and 6.5±0.9 points respectively and significantly differed from the values of the “Intact” group (1±0.6). According to the Neurological impairment assessment, these correspond to a moderate CNS injury. In most cases, the changes are associated with muscle dystrophy, reduced pain reflexes, and anterior limb paralysis (left-hemispheric ischemia 70% of cases; right-hemispheric ischemia 100% of cases).

Histological studies of the brain cortex have not revealed any significant morphological changes in the “Intact” and “Sham-operated” groups. The cortex structure was represented mainly by cells of large and medium sizes with a rounded shape and clear contour. Normochrome neurons had a large nucleus located on the main part of the cell (Fig. 2).

Ischemia modeling causes structural changes in the brain matter. Analysis of morphometric parameters of neurons on day 60 of the pot-ischemic period showed that approximately 10% of cells in the “Left-hemispheric ischemia” and “Right-hemispheric ischemia” groups were enlarged in diameter; neurons with the peripheral nucleus are observed in the fields of view. The total number of hyperchromic neurons in 10 fields of view averaged 30-40%, while the number of bipolar neurons was 5-7%. The prevailing part of cells lost the clarity of contours and deformed; approximately 20% of cells had a polygon form. The brain cells were losing their spherical shape; cell nuclei were lengthened.

The brain structures lesions in the “Left-hemispheric ischemia” and “Right-hemispheric ischemia” groups were similar. However, in the group with left common carotid artery occlusion, a large number of dilated capillaries and hemorrhage areas were clearly detected. On the other hand, in the group with the right common carotid artery occlusion, perivascular tissue edema was more pronounced. These observations emphasize the qualitative changes in brain tissue after ischemic injury.

Table 4

Spatial memory assessment in mice in the early post-ischemic period

Experimental groups	Novel object recognition test		Object relocation test	
	Discrimination coefficient	Time spent around novel object, s	Discrimination coefficient	Time spent around relocated object, s
Intact	0.8±0.03	163.7±3.3	0.8±0.03	160.3±2.8
Sham-operated	0.8±0.01	138.3±19.2	0.7±0.5	125.6±13.2
Left-hemispheric ischemia	0.2±0.05*	68.0±21.4*	0.2±0.1	66.7±23.7*
Right-hemispheric ischemia	0.7±0.2	86.5±20.1*	-0.1±0.05*	34.7±16.5*

* – versus “Intact”, $p < 0.05$, ANOVA

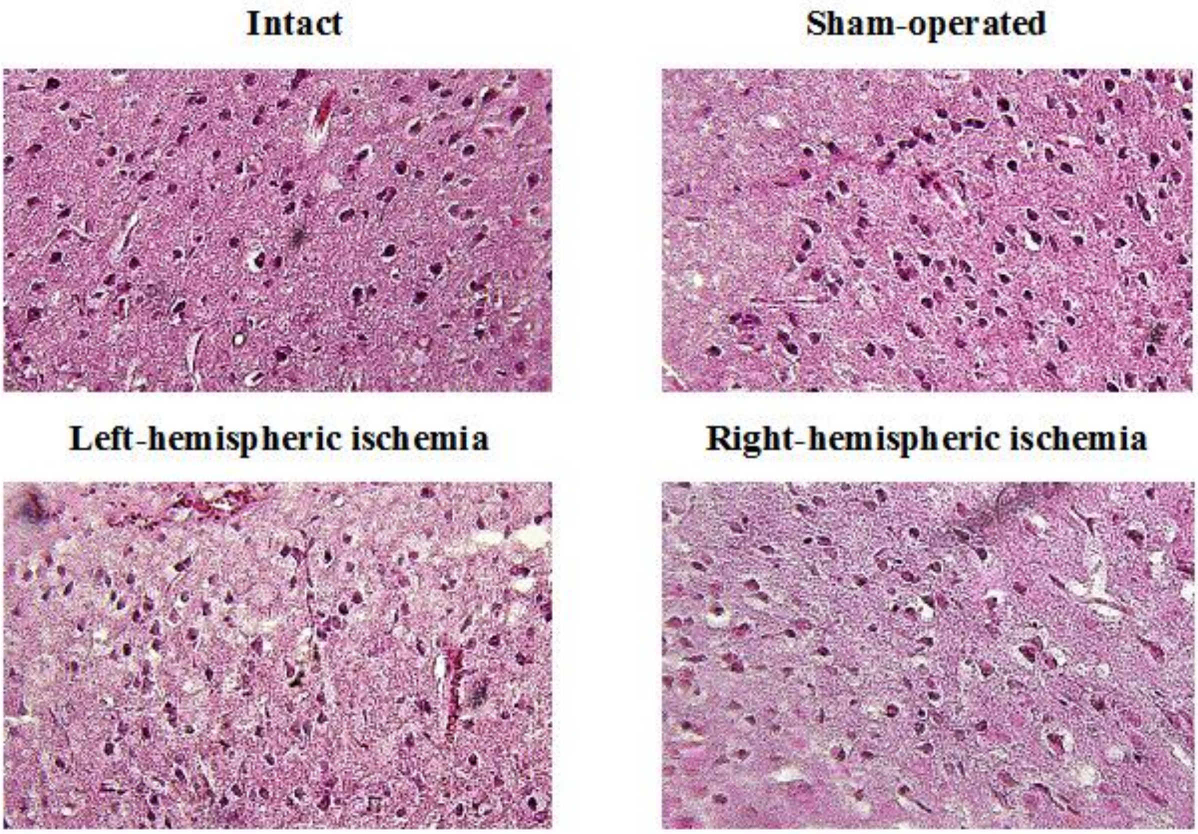

Fig. 2. Representative images of histological samples of murine brain cortex on day 60 of the post-ischemic period. Hematoxylin-eosin staining, magnification x20

Table 5

Neurological status and parameters of behavioral reactions of mice in the "Open field" test on day 60 of the post-ischemic period

Experimental groups	Neurological status (points)	Acts of defecation	Acts of urination	Acts of grooming	UP	SQ, periphery	SQ, center	T, center, s	Number of mink reflex
Intact	1,0±0,6	1,0±0,6	0,33±0,1	7,0±3,5	3,0±1,5	25,3±7,1	7,3±3,3	33±8,4	18,3±6,6
Sham-operated	4,0±1,9	1,0±0,6	1,3±0,8	17,3±2,9	6,0±2,5	48,3±11,1	12±3,0	32,3±15,6	17,6±2,3
Left-hemispheric ischemia	**6,0±0,5***	2,6±0,6	0,28±0,1	9,28±2,4	6,4±2,5	37,14±13,3	5,14±1,4	**96,7±32,6***	13,7±3,6
Right-hemispheric ischemia	**6,5±0,9***	2,0±1,1	1,0±0,4	**17,0±5,2***	5,5±0,3	44±4,2*	3,25±0,9	**4,75±1,1***	15,25±3,7

UP – the number of upright postures, SQ – the number of crossed squares, T – time spent in the arena center.
* – versus "Intact", $p < 0.05$, ANOVA

Discussion

This study provides a comparative analysis of the severity of morpho-functional disorders in C57BL/6J mice brain depending on the location of the ischemic lesion site.

It was shown that focal ischemia modeling using the right common carotid artery occlusion leads to a significant loss of animal body weight during 14 days of the post-ischemic period. In animals with left common carotid artery occlusion the decreased body weight was registered only on the first day of the post-ischemic period, which is consistent with previous studies showing the postoperative weight recovery in mice within the next seven days after surgery (Park et al., 2014). Using an experimental model of focal ischemia by the internal carotid artery occlusion, it was found that hypoperfusion affects the lingual, facial and maxillary arteries, causing ischemic damage to chewing muscles (Pang et al., 2020; Fréchou et al., 2019; Wiesmann et al., 2017) and causing disturbances in food and water consumption (Boyko et al., 2010). It could be assumed that the loss of body weight in case of the right common carotid artery occlusion is mediated by damage to adventitious arteries provided oxygen and nutrients to facial and chewing muscles which in turn involved in chewing and swallowing.

Simulation of left- and right-sided focal ischemia leads to neurological status impairments and anterior limb muscular dystrophy. Neurological deficit was primarily mediated by the development of anterior limb paralysis and ptosis. Within two experimental groups, ipsilateral paralysis was recorded in 75% of cases and contralateral paralysis in 25% of cases. The development of anterior limb paralysis leads to disruption of motor function and muscle dystrophy, which was confirmed by the data on Hanging wire test.

The development of ipsilateral ptosis was observed in animals with both right and left common carotid artery occlusion, but it was more pronounced in the “Right-hemispheric ischemia” group (day 14 after surgery: Left-hemispheric ischemia 25% of cases, Right-hemispheric ischemia 100% of cases). Majdan shows that ptosis occurs as a result of the 3rd cranial nerve (oculomotor nerve) compression induced by cerebral edema or formation of a non-calorie hernia (Majdan et al., 2015).

Ischemic brain damage via the common carotid artery occlusion leads to disturbances in spatial memory and research activity in animals. Interestingly, that the preference to study novelty is mainly reduced in the “Left-hemispheric ischemia” group, whereas spatial memory disturbances were observed primarily in the “Right-hemispheric ischemia” group. It was previously shown that a 30-minute episode of brain ischemia significantly reduced the population of neurons in medial striatum involved in the processes of remembrance the exact location of objects (navigation) (Ermine et al., 2019; Somaa et al., 2017; Korzhevsky et al., 2009). Development of inflammation, oxidative stress and hypoxia in the ischemic site can also cause the death of neurons responsible for storage and reproduction of information (Jayaraj et al., 2019; Lee et al., 2015; Denes et al., 2010).

The motor and reflexive activity disorders in mice with left or right common carotid artery occlusion maintained in the remote post-ischemic period. Of note, the animals in the “Left-hemispheric ischemia” group also had a latent level of emotional tension. These alterations were accompanied by morphological changes, characterized by a large number of dilated capillaries and hemorrhage areas in the case of left common carotid occlusion and pronounced perivascular tissue edema in the case of right common carotid occlusion.

It is known that compensation of functional deficit in the ischemic injury of one of the hemispheres is realized through symmetrical structures of the other hemisphere. However, localization of ischemic lesion site could have a significant impact on specificity and speed of the rehabilitation period.

For instance, Dittmar with co-authors showed that external carotid artery occlusion in rats induced myopathy characterized by long-term motor system dysfunction. In combination with facial and chewing muscles dysfunction, resulting in malnutrition and dehydration, this caused slower recovery of locomotor functions

(Dittmar et al., 2003). Using a rat middle cerebral artery occlusion model, it was shown that lesions in the left hemisphere induce more severe sensorimotor disturbances, while pronounced cognitive violations were observed when the right hemisphere is affected (Zhai & Feng, 2018).

A number of clinical studies indicate that prognosis for recovery in patients with left-hemispheric ischemic stroke is more favorable. At localization of ischemic site in the left hemisphere, the interhemispheric relations recover more quickly; if it is located in the right hemisphere, the intensive recovery of intrahemispheric relations are observed. More active memory restoration is shown for left-hemispheric stroke, the psycho-emotional sphere recovery for the right-hemispheric stroke (Hedna et al., 2013; Rastogi et al., 2015; Vahid-Ansari et al., 2016).

In the current study, we characterized the features of ischemic brain injury outcome in mice depending on the right or left common carotid artery occlusion. The right-hemispheric focal ischemia decreases the body weight, causes spatial memory impairment, activates the development of a pronounced long-term neurological deficit characterized by ipsilateral limb paralysis, ptosis and muscle dystrophy, which is accompanied by perivascular brain tissue edema. In the left-hemispheric focal ischemia, the neurological status impairments are also observed, but they less pronounced than in case of right hemispheric ischemia. Moreover, preference to study novelty is reduced, and long-term emotional strain is revealed. The peculiarity of ischemic injury using the left common carotid artery occlusion is accompanied by the presence of hemorrhages and dilated capillaries in the damaged brain hemisphere.

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Authors declare no conflicts of interests.

References

BOYKO M., ZLOTNIK A., GRUENBAUM B.F., GRUENBAUM S.E., OHAYON S., GOLDSMITH T., KOTZ R., LEIBOWITZ A., SHEINER E., SHAPIRA Y. & TEICHBERG VI. (2010): An experimental model of focal ischemia using an internal carotid artery approach. Journal of neuroscience methods, 193(2), 246–253. doi:10.1016/j.jneumeth.2010.08.026

CANAZZA A., MINATI L., BOFFANO C., PARATI E. & BINKS S. (2014): Experimental Models of Brain Ischemia: A Review of Techniques, Magnetic Resonance Imaging, and Investigational Cell-Based Therapies. Frontiers in neurology, 5, 19. https://doi.org/10.3389/fneur.2014.00019

DERE E., HUSTON J.P. & DE SOUZA SILVA M.A. (2007): The Pharmacology, Neuroanatomy and Neurogenetics of One-Trial Object Recognition in Rodents. Neuroscience and Biobehavioral Reviews, 31, 673–704. https://doi.org/10.1016/j.neubiorev.2007.01.005.

DENES A., THORNTON P., ROTHWELL N.J. & ALLAN S.M. (2010): Inflammation and brain injury: acute cerebral ischaemia, peripheral and central inflammation Brain, behavior, and immunity, 24(5), 708–723. https://doi.org/10.1016/j.bbi.2009.09.010.

DITTMAR M., SPRUSS T., SCHUIERER G. & HORN M. (2003): External carotid artery territory ischemia impairs outcome in the endovascular filament model of middle cerebral artery occlusion in rats. Stroke, 34(9), 2252–2257. https://doi.org/10.1161/01.STR.0000083625.54851.9A.

DONKOR E.S. (2018): Stroke in the 21st Century: A Snapshot of the Burden, Epidemiology, and Quality of Life. Stroke research and treatment, 2018, 3238165. doi: 10.1155/2018/3238165.

ERMINE C.E., SOMAA F.A., WANG T.Y., KAGAN B.J., PARISH C.L. & THOMPSON L.H. (2019): Long-term motor deficit and diffuse cortical atrophy following focal cortical ischemia in athymic rat. Frontiers in cellular neuroscience, 13, 552. https://doi.org/10.3389/fncel.2019.00552.

FRÉCHOU M., MARGAILL I., MARCHAND-LEROUX C. & BERAY-BERTHAT V. (2019): Behavioral tests that reveal long-term deficits after permanent focal cerebral ischemia in mouse. Behavioural brain research, 360, 69–80. https://doi.org/10.1016/j.bbr.2018.11.040.

GORELICK P. B. (2019): The global burden of stroke: persistent and disabling. The Lancet Neurology, 18(5), 417-418, doi: 10.1016/S1474-4422(19)30030-4.

HEDNA V.S., BODHIT A.N., ANSARI S., FALCHOOK A.D., STEAD L., HEILMAN K. M. & WATERS M.F. (2013): Hemispheric differences in ischemic stroke: is left-hemisphere stroke more common? Journal of clinical neurology (Seoul, Korea), 9(2), 97–102. doi: 10.3988/jcn.2013.9.2.97.

HOFFMAN E. & WINDER S.J. (2016): A Modified Wire Hanging Apparatus for Small Animal Muscle Function Testing. PLoS currents, 8, ecurrents.md.1e2bec4e78697b7b0ff80ea25a1d38be. https://doi.org/10.1371/currents.md.1e2bec4e78697b7b0ff80ea25a1d38be

JAYARAJ R.L, AZIMULLAH S., BEIRAM R., JALAL F.Y. & ROSENBERG GA. (2019): Neuroinflammation: friend and foe for ischemic stroke. Journal of neuroinflammation, 16(1), 142. https://doi.org/10.1186/s12974-019-1516-2.

KATAN M. & LUFT A. (2018): Global Burden of Stroke. Seminars in neurology, 38(2), 208–211. https://doi.org/10.1055/s-0038-1649503.

KAYA A.H., ERDOGAN H. & TASDEMIROGLU E. (2017): Searching evidences of stroke in animal models: a review of discrepancies. Turkish neurosurgery, 27(2), 167–173. https://doi.org/10.5137/1019-5149.JTN.15373-15.2.

KIRKMAN M.A. & SMITH M. (2016): Brain Oxygenation Monitoring. Anesthesiology clinics, 34(3), 537–556. https://doi.org/10.1016/j.anclin.2016.04.007.

KORZHEVSKY D.E., VLASOV T.D., KIRIK O.V. & SUKHORUKOVA E.G. (2009): Selective death of the striatum neurons in rats after the transient occlusion of the middle cerebral artery. Morfologiya, 2, 80-82.

KUL'CHIKOV A.E., MAKARENKO A.N., NOVIKOVA YU.L. & DOBYCHINA E.E. (2008): Sposob opredeleniya nevrologicheskogo defitsita u melkikh laboratornykh zhivotnykh pri porazhenii golovnogo mozga. A.s. 2327227 C2 [Neurologic impairment determination method in small laboratory animals with brain lesions. A.c. 2327227 C2. 2008].

KUMAR A, AAKRITI & GUPTA V. (2016): A review on animal models of stroke: An update. Brain research bulletin, 122, 35–44. https://doi.org/10.1016/j.brainresbull.2016.02.016.

LEE W., MOON M., KIM H.G., LEE T.H. & OH M.S. (2015): Heat stress-induced memory impairment is associated with neuroinflammation in mice. Journal of neuroinflammation, 12, 102. https://doi.org/10.1186/s12974-015-0324-6.

LI Z., CHU Z., ZHAO S., MA L., YANG Q., HUANG X. & ZHOU Z. (2019): Severe Stroke Patients With Left-Sided Occlusion of the Proximal Anterior Circulation Benefit More From Thrombectomy. Frontiers in neurology, 10, 551. https://doi.org/10.3389/fneur.2019.00551.

LIVINGSTON-THOMAS J.M., JEFFERS M.S., NGUEMENI C., SHOICHET M.S., MORSHEAD C.M. & CORBETT D. (2015): Assessing cognitive function following medial prefrontal stroke in the rat. Behavioural brain research, 294, 102–110. https://doi.org/10.1016/j.bbr.2015.07.053.

MACHINSKIJ P.A., PLOTNIKOVA N.A., UL"JaNKIN V.E., KEMAJKIN S.P. & RYBAKOV A.G. (2019): Sravnitel'naja harakteristika pokazatelej smertnosti i letal'nosti ot ishemicheskogo i gemorragicheskogo insul'tov v Rossii. Izvestija vysshih uchebnyh zavedenij. Povolzhskij region, 3(51), 101-118 [in Russian].

MAJDAN M., STEYERBERG E.W., NIEBOER D., MAURITZ W., RUSNAK M. & LINGSMA H.F. (2015): Glasgow coma scale motor score and pupillary reaction to predict six-month mortality in patients with traumatic brain injury: comparison of field and admission assessment. Journal of neurotrauma, 32(2), 101–108. https://doi.org/10.1089/neu.2014.3438.

MCCLUSKEY G., WADE C., MCKEE J., MCCARRON P., MCVERRY F. & MCCARRON M. O. (2016): Stroke Laterality Bias in the Management of Acute Ischemic Stroke. Journal of stroke and cerebrovascular diseases, 25(11), 2701–2707. https://doi.org/10.1016/j.jstrokecerebrovasdis.2016.07.019

MITROSHINA E.V., ABOGESSIMENGANE B.ZH., URAZOV M.D., HAMRAOUI I., MISHCHENKO T.A., ASTRAKHANOVA T.A., SHCHELCHKOVA N.A., LAPSHIN R.D., SHISHKINA T.V., BELOUSOVA I.I., MUKHINA I.V. & VEDUNOVA M.V. (2017): Adaptive role of glial cell line-derived neurotrophic factor in cerebral ischemia. Sovremennye tehnologii v medicine. 9(1), 68–77, https://doi.org/10.17691/stm2017.9.1.08.

OJAGHIHAGHIGHI S., VAHDATI S.S., MIKAEILPOUR A. & RAMOUZ A. (2017): Comparison of neurological clinical manifestation in patients with hemorrhagic and ischemic stroke. World journal of emergency medicine, 8(1), 34–38. https://doi.org/10.5847/wjem.j.1920-8642.2017.01.006.

PANG Q., WU Q., HU X., ZHANG J. & JIANG Q. (2020): Tooth loss, cognitive impairment and chronic cerebral ischemia. Journal of dental sciences, 15(1), 84–91. https://doi.org/10.1016/j.jds.2019.09.001.

PARK S.Y., MARASINI S., KIM G.H., KU T., CHOI C., PARK M.Y., KIM E.H., LEE Y.D., SUH-KIM H. & KIM S.S. (2014): A method for generating a mouse model of stroke: evaluation of parameters for blood flow, behavior, and survival [corrected]. Experimental neurobiology, 23(1), 104–114. https://doi.org/10.5607/en.2014.23.1.104.

PORTEGIES M.L., SELWANESS M., HOFMAN A., KOUDSTAAL P.J., VERNOOIJ M W. & IKRAM M.A. (2015): Left-sided strokes are more often recognized than right-sided strokes: the Rotterdam study. Stroke, 46(1), 252–254. https://doi.org/10.1161/STROKEAHA.114.007385.

RASTOGI V., LAMB D.G., WILLIAMSON J.B., STEAD T.S., PENUMUDI R., BIDARI S., GANTI L., HEILMAN K.M. & HEDNA V.S. (2015): Hemispheric differences in malignant middle cerebral artery stroke. Journal of the neurological sciences, 353(1-2), 20–27. https://doi.org/10.1016/j.jns.2015.04.036.

SHIMODA K. & ROBINSON R.G. (1998): Effects of anxiety disorder on impairment and recovery from stroke. The Journal of neuropsychiatry and clinical neurosciences, 10(1), 34–40. https://doi.org/10.1176/jnp.10.1.34.

Somaa F.A., Wang T.Y., Niclis J.C., Bruggeman K.F., Kauhausen J.A., Guo H., McDougall S., Williams R.J., Nisbet D.R., Thompson L.H. & Parish C.L. (2017): Peptide-based scaffolds support human cortical progenitor graft integration to reduce atrophy and promote functional repair in a model of stroke. Cell Rep., 20, 1964-1977.

TADI P. & LUI F. Acute Stroke (Cerebrovascular Accident). StatPearls Publishing 2020. https://www.ncbi.nlm.nih.gov/books/NBK535369/

VAHID-ANSARI F., LAGACE D.C. & ALBERT P. R. (2016): Persistent post-stroke depression in mice following unilateral medial prefrontal cortical stroke. Translational psychiatry, 6(8), e863. https://doi.org/10.1038/tp.2016.124

VASIL"EV I.A., STUPAK V.V., ChERNYH V.A., ZAJDMAN A.M., POLOVNIKOV E.V., ChERNYH E.R., ShEVELA E.Ja. & DERGILEV A.P. (2015): Jeksperimental'nye modeli sosudistyh porazhenij golovnogo mozga (obzor literatury). Uspehi sovremennogo estestvoznanija, 1-3, 366-369 [in Russian].

VEJN A.M., VOZNESENSKAJA T.G., GOLUBEV V.L. & DJUKOVA G.M. (2007): Depressija v nevrologicheskoj praktike. Moskva: MIA, 197 pp. [in Russian].

WALTER L. (1995): Recovery from stroke involving the left middle cerebral artery. Modern Psychological Studies. 3(2), 21-28.

WIESMANN M., ZINNHARDT B., REINHARDT D., ELIGEHAUSEN S., WACHSMUTH L., HERMANN S., DEDEREN P.J., HELLWICH M., KUHLMANN M.T., BROERSEN L.M., HEERSCHAP A., JACOBS A.H. & KILIAAN A.J. (2017): A specific dietary intervention to restore brain structure and function after ischemic stroke. Theranostics, 7(2), 493–512. https://doi.org/10.7150/thno.17559.

ZHAI Z. & FENG J. (2018): Left-right asymmetry influenced the infarct volume and neurological dysfunction following focal middle cerebral artery occlusion in rats. Brain and behavior, 8(12), e01166. https://doi.org/10.1002/brb3.1166