Myronov O. O. Mnestic functions restoration due to chronic brain ischemia pathogenetically oriented pharmacocorrection as a condition to enhance cerebral resistance. Journal of Education, Health and Sport. 2025;85:70620. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2025.85.70620
https://apcz.umk.pl/JEHS/article/view/70620
https://zenodo.org/records/19440219

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences);
Health Sciences (Field of medical and health sciences). Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).© The Authors 2025;
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The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 22.08.2025. Revised: 28.08.2025. Accepted: 19.09.2025. Published: 25.09.2025.

UDK 616.8-009.12-008.6-036.12-06

MNESTIC FUNCTIONS RESTORATION DUE TO CHRONIC BRAIN ISCHEMIA PATHOGENETICALLY ORIENTED PHARMACOCORRECTION AS A CONDITION TO ENHANCE CEREBRAL RESISTANCE

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Abstract

The purpose of the study was to investigate the efficacy of separate and combined administration of pentoxifylline, memantine and xavron in the pharmacological correction of cognitive impairment in rats under conditions of experimental chronic brain ischemia. The experimental trials were performed in conditions of chronic brain ischemia in 80 male rats. Animals were observed during 7 days after carotid artery ligation. The processes of learning, short-tern and long-term memory expression together with conditioned reflexes extinction were determined 1, 3, 5 and 7 days from the beginning of the trials. The efficacy of neuroprotection in case of endonasal pentoxifylline and i.p. memantine and xavron separate and combined administration was evaluated in the modeled conditions. Rats with chronic brain ischemia were shown to develop mnestic disturbances, and their severity is time-dependent. The severity of the developed cognitive disorders is characterized by impairment of learning processes and of short- and long-term memory functioning. The positive effects of separate and combined use of pentoxifylline, memantine, and xavron under chronic brain ischemia conditions contributed to restoration of mnestic disturbances. The efficacy of the tested neuroprotection regimens under

the experimental conditions was dependent on the duration of the post-ischemic period and on the routes of administration of the pharmacological agents. The most effective method of pharmacological correction of cognitive disorders under chronic brain ischemia conditions is combined pentoxifylline+ memantine administration as well as pentoxifylline+ xavron administration. The third place in terms of neuroprotective efficacy is occupied by endonasal pentoxifylline administration. The nootropic efficacy of these treatment regimens was recorded as early as Day 3 of the experiment and persisted until the end of the experiment. The author conclude that a number of functional disturbances established under chronic brain ischemia conditions constitute evidence of weakened cerebral resistance and an impetus for developing a comprehensive pathogenetically oriented correction of the formed disorders aimed at eliminating the developed disturbances and restoring cerebral resistance. He is confident that the nootropic efficacy of separate and combined administration of pentoxifylline, memantine and xavron in conditions of chronic brain ischemia enhances cerebral resistance, restores mnestic disturbances manifested by impairment of memory engram formation and retention, and serves as an experimental basis for the expediency of clinical testing of comprehensive pathogenetically substantiated correction of mnestic disorders in a large contingent of patients with chronic ischemia.

Keywords: cerebrovascular diseases; chronic brain ischemia; cerebral resistance; cognitive disorders; memory; learning; pathogenic mechanisms; pharmacological correction; neuroprotection.

One of the leading problems of modern medical science and, in particular, pathophysiology is the diagnosis, treatment, and prevention of cerebrovascular disorders, which over time have become an important medical, economic, and social problem [2, 6, 8, 18]. On the one hand, the importance of this issue is underscored by the accelerated aging of the world's population, which is accompanied by age-dependent damage to the cerebral gray matter, development of endothelial dysfunction, impaired cerebral blood supply, and, as a consequence, pronounced disorders of mnestic functions [7, 9, 22]. On the other hand, the age-dependent progressive impairment of cerebral circulation caused by the gradual accumulation of ischemic and secondary degenerative changes in the brain inevitably contributes to the development of clinical (and sometimes persistent subclinical) manifestations in the form of stable neurological deficit combined with emotional-personality and cognitive disorders.

From a fundamental standpoint, age-dependent ischemic and oxidative variants of neuronal death, together with a history of cerebrovascular episodes, in addition to all other changes, "trigger" a cascade of complex pathobiochemical, pathomorphological, and pathogenetic mechanisms, the final outcomes of which are irreversible demyelination, disturbances of synaptic mechanisms and neuronal interaction, and impaired neurotransmitter synthesis [2, 11]. All of the above contributes to initial or pronounced manifestations of cognitive impairment, the development of which is always age-dependent and represents a consequence (and sometimes a harbinger) of chronic brain ischemia, as has been traced under clinical conditions and demonstrated in experimental observations [5, 13].

Clinicians recommend early diagnosis of cognitive impairment before the formation of neurological deficit, at which stage therapeutic efficacy decreases substantially. In cases of acute vascular catastrophe, mnestic impairment is an undesirable consequence of this pathological condition. From the standpoint of prospects for pharmacological correction of cognitive impairment, this most likely concerns secondary neuroprotection, since the most important task is the complete restoration of cerebral blood supply and the functional activity of vital organs and systems.

In addition to determining motor and emotional disorders under conditions of experimental reproduction of chronic brain ischemia [3], we also decided to study the specific features of conditioned reflex activity formation under these conditions and to assess the efficacy of the pharmacocorrection regimen we used for manifestations of chronic brain ischemia, involving systemic and endonasal administration of a number of drugs with a complex mechanism underlying restorative and cytoprotective action.

The aim of the study was to investigate the efficacy of separate and combined administration of pentoxifylline, memantine, and xavron in the pharmacological correction of cognitive impairment in rats under conditions of experimental chronic brain ischemia.

Materials and Methods

Animals.

The experiments were carried out as a chronic study in 80 white male rats weighing 180-220 g and housed under vivarium conditions. Animal maintenance, handling, and manipulations were performed in accordance with the "General Ethical Principles of Animal Experiments" adopted by the VI National Congress on Bioethics (Kyiv, 2019), as well as the recommendations of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1985), the methodological recommendations of the State Pharmacological Center of the Ministry of Health of Ukraine

"Preclinical Studies of Drugs" (2001), and the rules of humane treatment of experimental animals.

The model of chronic brain ischemia (CBI) was reproduced by skin incision, isolation, and bilateral ligation of the carotid arteries [2, 10].

Animals randomization.

The following groups of animals were distinguished: Group 1, control (intact rats in which only the skin was incised and the carotid arteries were not ligated, n=9); Group 2, experimental (rats with reproduced CBI, n=16). Rats of Group 3 with CBI received pentoxifylline (PF; Darnytsia, Ukraine; 2.0%, endonasally, 10 μL, n=11). Rats of Group 4 with CBI received memantine (MEM; InterChem, 10 mg/kg, intraperitoneally, n=11). Rats of Group 5 with CBI received Xavron (XA; Yuria-Pharm, Ukraine; 100 mg/kg, intraperitoneally, n=11). Rats of Group 6 (n=11) with CBI received PF and MEM in combination. Rats of Group 7 (n=11) with CBI received PF and XA in combination.

After carotid artery ligation, the rats were observed for 7 days. During this period, the severity of mnestic function impairment was assessed.

Experimental tests used.

In the first series of experiments, the ability of rats to develop and retain a conditioned active avoidance response (CAAR) [21] was studied, whereas in the second series the specific features of the conditioned food reflex under the applied experimental conditions were determined [12].

Statistical procedures.

The obtained data were analyzed using Bonferroni parametric criterion and Kruskal–Wallis nonparametric criterion. The minimum statistical probability was determined at $p<0.05$.

Results

1. Effect of Separate and Combined Administration of Pentoxifylline, Memantine, and Xavron on Learning and Memory Processes in Rats with CBI

The animals were first presented with a conditioned stimulus and, 5 s later, an unconditioned stimulus. After a series of electric shocks, the animal initially froze and then attempted to escape from the electric stimulation. At first, rats in the control group required 17-22 s to reach the goal, after which the running time decreased. An anticipatory response developed: after presentation of the conditioned stimulus, the animal moved to the opposite side before receiving the electric stimulus. Consolidation of the anticipatory response served as the criterion for CAAR formation.

Beginning on Day 1 after reproduction of CBI, the number of pairings of the conditioned and unconditioned stimuli required for CAAR development was 43.5% higher than in the control observations ($p<0.05$, Table 1). The values of the studied parameter in rats with CBI that received separate administration of PF, MEM, and XA were comparable with those in rats with CBI without pharmacological correction and remained significantly higher than the corresponding values in the control group ($p<0.05$). In rats with CBI that received combined administration of PF and MEM, as well as PF and XA, the studied parameter was 30.1±2.5 and 30.6±2.2, respectively, which exceeded the corresponding values in intact rats by only 11.9% and 13.8% and did not differ from the analogous indices in rats with CBI that received separate administration of the indicated drugs (in all cases $p>0.05$).

On Day 3 of the experiment, in the group of rats with endonasal PF administration, the number of conditioned/unconditioned stimulus pairings required for CAAR development was 1.47-fold lower than in rats with CBI without treatment ($p<0.05$). In the groups of rats with CBI that received combined PF+MEM and PF+XA, this index was 28.1±2.2 and 29.3±2.0, respectively, and also differed significantly from the value in rats with CBI without pharmacological correction (in all cases $p<0.05$). In the other groups, the studied parameters, while exceeding the control values ($p<0.05$), did not differ statistically from those in rats with CBI without treatment ($p>0.05$).

On Day 5 of the experiment, the number of conditioned/unconditioned stimulus pairings required for CAAR development in the group of rats with CBI receiving endonasal PF was 42.7% lower than the corresponding index in the group of rats with CBI without pharmacological correction ($p<0.05$). In the groups of rats with CBI receiving combined PF+MEM and PF+XA, the registered values were 28.0±2.6 and 28.6±2.0, respectively, which were 50% and 38% lower than the corresponding values in rats with CBI without treatment and, at the same time, 34.3% and 22.3% lower, respectively, than the analogous data in rats with CBI that received MEM and XA separately (in all cases $p<0.05$).

A similar trend in learning performance under CBI and administration of the indicated drugs was also noted on Day 7 of the post-ischemic period.

When studying changes in short-term memory resulting from ischemic brain injury, it was found that the number of conditioned/unconditioned stimulus pairings required for CAAR development 1 day after formation of the conditioned response in rats with CBI was 77.8% higher than in the control group ($p<0.05$).

Table 1 - Effect of Separate and Combined Administration of Pentoxifylline (PF), Memantine (MEM), and Xavron (XA) on Learning, Short-Term Memory, and Long-Term Memory in Rats with CBI

Animal groups	Number of pairings of the conditioned stimulus and unconditioned stimulus required for CAAR development		
	Learning	Short-term memory	Long-term memory
Day 1			
Group 1 – Control, n=9	26.9±2.8	8.1±0.8	3.2±0.4
Group 2 – CBI, n=16	38.6±3.4*	14.4±1.1*	6.6±0.8*
Group 3 – CBI + PF, n=11	33.4±3.3*	11.6±1.2*	5.3±0.3
Group 4 – CBI + MEM, n=11	38.3±3.1*	12.9±0.9*	6.0±0.7*
Group 5 – CBI + XA, n=11	37.6±3.2*	12.3±1.2*	5.8±0.5*
Group 6 – CBI + PF + MEM, n=11	30.1±2.5	10.6±0.8	4.8±0.2
Group 7 – CBI + PF + XA, n=11	30.6±2.2	11.4±0.7	5.4±0.3
Day 3			
Group 1 – Control, n=9	27.2±2.8	7.6±0.7	3.0±0.5
Group 2 – CBI, n=13	44.5±3.3*	19.6±1.5*	9.3±0.6*
Group 3 – CBI + PF, n=9	30.3±2.2#	10.6±0.8#	5.7±0.3*#
Group 4 – CBI + MEM, n=9	38.5±3.0*	12.2±1.2	8.6±0.5*
Group 5 – CBI + XA, n=8	36.0±2.9*	11.3±1.3	7.9±0.6*
Group 6 – CBI + PF + MEM, n=10	28.1±2.2#	9.7±0.8#	4.5±0.4# @
Group 7 – CBI + PF + XA, n=8	29.3±2.0#	10.4±0.6#	4.3±0.3# @
Day 5			
Group 1 – Control, n=9	27.2±2.6	7.6±0.7	2.8±0.4
Group 2 – CBI, n=12	42.1±3.2*	19.0±1.4*	8.1±0.6*
Group 3 – CBI + PF, n=9	29.5±2.6#	9.6±0.6#	5.5±0.2#
Group 4 – CBI + MEM, n=9	37.6±2.8*	11.4±0.8	6.4±0.6*
Group 5 – CBI + XA, n=7	35.1±2.5*	11.0±0.7	6.3±0.3*
Group 6 – CBI + PF + MEM, n=10	28.0±2.6# @	8.6±0.6#	4.1±0.4# @
Group 7 – CBI + PF + XA, n=8	28.6±2.0# @	9.9±0.4#	4.8±0.3# @
Day 7			
Group 1 – Control, n=9	26.8±2.5	7.6±0.6	3.2±0.3
Group 2 – CBI, n=12	38.1±3.2*	15.3±1.2*	7.9±0.4*
Group 3 – CBI + PF, n=9	29.0±3.1#	9.2±0.5#	4.1±0.5#
Group 4 – CBI + MEM, n=9	32.0±2.5	10.1±0.8	5.2±0.3
Group 5 – CBI + XA, n=7	34.7±2.6	10.9±0.7	4.6±0.5
Group 6 – CBI + PF + MEM, n=10	26.2±2.4# @	8.4±0.4#	3.8±0.4# @
Group 7 – CBI + PF + XA, n=8	26.1±2.5# @	8.8±0.5#	4.4±0.3# @

Designation (in Tables 1 and 2): the decrease in the number of rats in the groups occurred because of animal death

Notes (in Tables 1 and 2):

* - $p<0.05$ – significant differences in the studied parameters compared with the corresponding values in the control group of animals;

- $p<0.05$ – significant differences in the studied parameters compared with the corresponding values in rats with chronic brain ischemia without pharmacological correction;

@ - $p<0.05$ – significant differences in the studied parameters compared with the corresponding values in rats with chronic brain ischemia that received pentoxifylline and/or memantine.

During the first day of the experiment, only in the groups of rats with CBI receiving combined PF+MEM and PF+XA administration did the value of the studied parameter not differ significantly from the control measurements ($p>0.05$).

On Day 3 of the experiment, the number of conditioned/unconditioned stimulus pairings required for CAAR development 1 day after conditioned response formation in the groups of rats with CBI receiving endonasal PF was 10.6±0.8, which was 1.85-fold lower than in rats with CBI without treatment ($p<0.05$). In the groups of rats receiving combined administration of the indicated drugs, the studied parameter was comparable with the corresponding control values ($p>0.05$) and was 2-fold and 1.89-fold lower than in rats with CBI without pharmacological correction (in all cases $p<0.05$).

Similar results, demonstrating greater efficacy of short-term memory recovery in rats with CBI due to endonasal PF administration, as well as combined PF+MEM and PF+XA treatment, were recorded until the end of the experiment.

When tracing the severity of long-term memory impairment over the course of the post-ischemic period, we recorded a twofold increase in the number of conditioned/unconditioned stimulus pairings required for CAAR development 7 days after conditioned response formation, indicating marked deterioration of long-term memory ($p<0.05$).

On Day 3 of the experiment, the number of conditioned/unconditioned stimulus pairings required for CAAR development 7 days after conditioned response formation in the group of rats with CBI receiving endonasal PF was 5.7±0.3, which was 63% lower than in rats with CBI without treatment ($p<0.05$). In the groups of rats with CBI receiving combined PF+MEM and PF+XA, the value of the studied parameter was not only lower than the corresponding value in rats with CBI without pharmacocorrection, but was also 56.1% and 31.3% lower, respectively, than in the groups of rats with CBI that received only separate administration of these drugs (in all cases $p<0.05$).

A similar pattern of data, proving a more pronounced efficacy of long-term memory recovery in rats with CBI as a result of endonasal PF administration and combined PF with MEM and XA, was obtained on Days 5 and 7 of the experiment (in all cases $p<0.05$).

The absolute values of the integral “retention” index calculated over the course of the post-ischemic period revealed its first significant changes on Day 3 of the experiment, when this index in rats with CBI was 28.8% lower than the corresponding value in intact rats (Fig. 1; $p<0.05$).

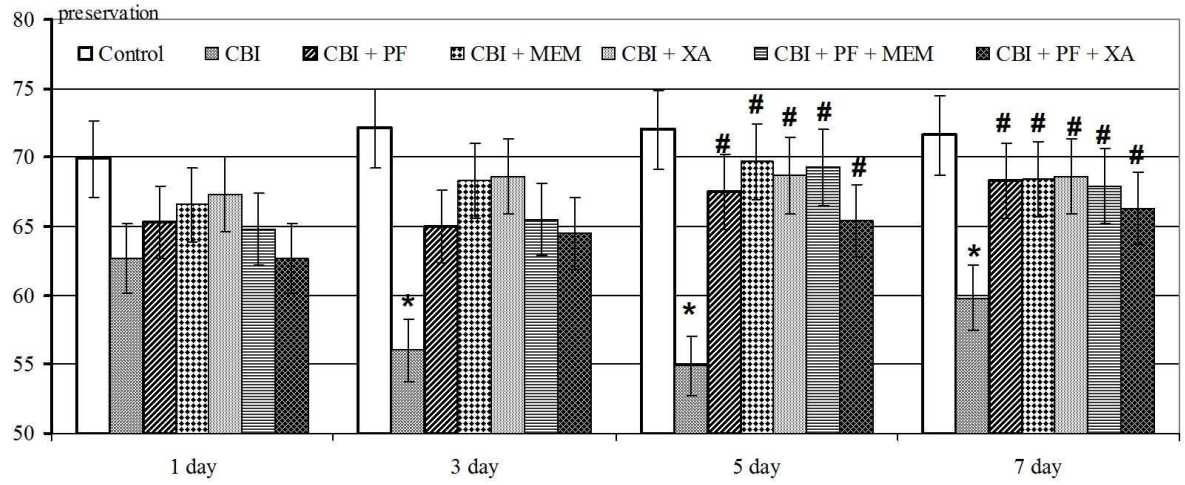

Figure 1. Effect of Separate and Combined Administration of Pentoxifylline (PF), Memantine (MEM), and Xavron (XA) on the "Retention" Index in Rats with CBI

Notes:

* – $p<0.05$ – significant differences in the studied parameters compared with the corresponding values in intact rats;

– $p<0,05$ – significant differences in the studied parameters compared with the corresponding values in rats with chronic brain ischemia without pharmacological correction.

Beginning on Day 5 of the post-ischemic period, the value of the "retention" index in all groups of rats with CBI that received the applied pharmacological drugs separately and in combination ranged from 65.4 to 69.7 units, which was statistically different from the analogous values in rats with CBI without treatment (in all cases $p<0.05$).

The observed dependence of a substantial increase in the absolute expression of the "retention" index on separate and combined administration of PF with MEM and XA was also recorded on Day 7 of the experiment, indicating effective pharmacocorrection of mnestic disorders in the post-ischemic period (in all cases $p<0.05$).

2. Effect of Separate and Combined Administration of Pentoxifylline, Memantine, and Xavron on Cognitive Dysfunction in Rats with CBI in the Conditioned Food Reflex Test

Twenty-four hours after bilateral carotid artery occlusion, the rats remained immobilized while staying in the center of the radial maze (Table 2).

The number of attempts to enter the maze arms before successful localization of food during learning began to appear on Day 3 of the post-ischemic period. This parameter in rats with CBI receiving endonasal PF was 0.6±0.1, which was significantly higher than the corresponding value in rats with CBI without pharmacocorrection, although it remained significantly lower than the analogous control value (in all cases $p<0.05$).

Table 2

Effect of Separate and Combined Administration of Pentoxifylline, Memantine, and Xavron on Conditioned Reflex Activity in Rats with CBI in the 8-Arm Radial Maze Test

Animal groups	Number of attempts to enter maze arms before successful localization of food during		
	Learning	Conditioned reflex retention	Conditioned reflex extinction
Day 1			
Group 1 – Control, n=9	7.4±0.6	0.9±0.1	1.1±0.1
Group 2 – CBI, n=16	0*	0*	0*
Group 3 – CBI + PF, n=11	0*	0*	0*
Group 4 – CBI + MEM, n=11	0*	0*	0*
Group 5 – CBI + XA, n=11	0*	0*	0*
Group 6 – CBI + PF + MEM, n=11	0*	0*	0*
7 група – ХІМ+ПФ+КСА, n=11	0*	0*	0*
Day 3			
Group 1 – Control, n=9	4.2±0.2	1.1±0.1	1.9±0.2
Group 2 – CBI, n=13	0*	0*	0*
Group 3 – CBI + PF, n=9	0.6±0.1*#	0.6±0.1#	0.5±0.1#
Group 4 – CBI + MEM, n=9	0	0.5±0.1#	0.5±0.1#
Group 5 – CBI + XA, n=8	0.4±0.1*	0.5±0.1#	0.4±0.1
Group 6 – CBI + PF + MEM, n=10	0.8±0.3*# @	0.9±0.1#	0.7±0.1#
Group 7 – CBI + PF + XA, n=8	0.6±0.2*#	0.7±0.1#	0.5±0.1#
Day 5			
Group 1 – Control, n=9	1.4±0.2	1.2±0.2	3.6±0.3
Group 2 – CBI, n=12	0.4±0.2*	0.5±0.2*	0*
Group 3 – CBI + PF, n=9	0.9±0.1#	1.1±0.1#	0.4±0.1#
Group 4 – CBI + MEM, n=9	0.6±0.1	0.8±0.1#	0.3±0.1#
Group 5 – CBI + XA, n=7	0.7±0.1	1.1±0.1#	0.3±0.1#
Group 6 – CBI + PF + MEM, n=10	1.2±0.2#@	1.2±0.2#	0.6±0.1#
Group 7 – CBI + PF + XA, n=8	0.9±0.1#	0.9±0.1#	0.5±0.1#
Day 7			
Group 1 – Control, n=9	1.2±0.1	1.1±0.1	4.2±0.3
Group 2 – CBI, n=12	0.4±0.2*	0.4±0.1*	0*
Group 3 – CBI + PF, n=9	1.1±0.1#	1.1±0.1#	0.3±0.1#
Group 4 – CBI + MEM, n=9	0.9±0.1#	0.9±0.1#	0.3±0.1#
Group 5 – CBI + XA, n=7	0.8±0.1#	0.9±0.1#	0.4±0.1#
Group 6 – CBI + PF + MEM, n=10	1.1±0.1#	1.1±0.1#	0.6±0.1#
Group 7 – CBI + PF + XA, n=8	0.9±0.1#	0.9±0.1#	0.4±0.1#

The value of the studied parameter in rats with CBI receiving combined PF+MEM reached 0.8±0.3, which was significantly higher than the corresponding values in rats with CBI without treatment and in rats with CBI receiving MEM alone (in all cases $p<0.05$). The studied parameter in the group receiving combined PF+XA was 0.6±0.2, which also showed

significant differences compared with the corresponding values in rats with CBI without pharmacocorrection and in rats with CBI receiving XA alone (in all cases $p<0.05$).

A similar pattern of results was also noted on Day 5 of the experiment.

On Day 7 of the post-ischemic period, the number of attempts to enter the maze arms before successfully finding food during learning in rats of all experimental groups with CBI and pharmacological correction significantly exceeded the corresponding values in rats with CBI without treatment (in all cases $p<0.05$).

When studying the specific features of conditioned reflex retention in the post-ischemic period, the absence of attempts by the animals to visit the radial maze arms in search of food was noted because of their immobilization.

On Day 3 of the experiment, the value of the studied parameter in rats of all groups with CBI receiving pharmacological correction exceeded the corresponding value in rats with CBI without treatment ($p<0.05$). The greatest number of attempts to enter the maze arms before successful localization of food during this period was demonstrated by rats with CBI receiving combined PF+MEM administration, which significantly exceeded the value in rats with CBI without treatment as well as the corresponding value in the group of rats with CBI receiving MEM alone (in all cases $p<0.05$).

The same trend in results was recorded by us up to Day 7 of the experiment.

To assess resistance to extinction of the conditioned reflex in animals with a previously formed food reflex in the 8-arm elevated radial maze test, a study was carried out without the use of food reinforcement. The dynamics of mnestic functions in the post-ischemic period were studied. As noted above, 24 hours after reproduction of CBI, the rats were immobilized, which made both their training and observation of conditioned reflex retention impossible.

Beginning on Day 3 of the post-ischemic period, the value of the studied parameter in all rats with CBI receiving pharmacological correction significantly exceeded the analogous value in rats with CBI without treatment (in all cases $p<0.05$). Similar results were recorded on Days 5 and 7 of the experiment.

Discussion

Thus, analysis of the obtained data allows the following conclusions to be drawn. In rats after carotid artery occlusion, mnestic disturbances are formed, the severity of which is time-dependent.

The severity of the developed cognitive disorders is characterized by impairment of learning processes and of short- and long-term memory functioning, involving modulation of

the entire neurophysiological arsenal underlying the formation, storage, and reinforcement of conditioned reflexes, with emphasis on neuronal, synaptic, and neurotransmitter mechanisms.

The adverse spectrum of mnestic dysfunctions recorded under the applied CBI model is emphasized by the methodological features of the study design, namely by the different models used to form and demonstrate conditioned reflexes in the conditioned active avoidance and conditioned food reflex tests. Under both applied tests, deterioration in the formation and retention of the conditioned reflex over the course of the post-ischemic period was proven. The integral "retention" index also confirmed the validity and correctness of the obtained results.

Another part of the obtained data demonstrates the positive effects of different regimens and routes of pentoxifylline, memantine, and Xavron administration under CBI conditions in terms of recovery of mnestic disturbances. It was established that the efficacy of the tested neuroprotection regimens in this study was dependent on the duration of the post-ischemic period and on the routes of administration of the pharmacological agents.

For discussion of the obtained results, we consider it appropriate to dwell on the following points. First, reproduction of cognitive disorders was not an end in itself from a methodological standpoint. Our data are consistent with existing clinical observations [14, 15, 17] and experimental studies [13, 20, 23], in which the specific features of reproduction, time characteristics, and clinical-psychological signs of cognitive impairment in patients with cerebrovascular diseases have been comprehensively investigated [16].

Second, the results obtained in this part of the study confirm previously proven data concerning adynamia and the formation of persistent neurological deficit in rats under conditions of ischemic brain injury [1, 3]. We remain steadfast supporters of the concept that the developed correction of ischemia-induced functional disorders must be pathogenetically determined. In this regard, we clearly understand that the mechanisms underlying the protective effects of the pharmacological agents selected for correction of mnestic disorders should be aimed at activating sanogenetic mechanisms that must necessarily be identified under the conditions of a specific pathological experimental state. In this context, we note that the previously established deficits of motor function, muscular activity, and emotional disturbances under CBI, together with the currently demonstrated pronounced impairment of conditioned reflex activity, substantially determine the state of ischemic damage to the brain parenchyma and provide convincing evidence of dysregulatory pathology with marked weakening of cerebral resistance. The latter factor – cerebral resistance – we regard as an integral indicator of the probable capacity to restore brain function under injury of various

origins, the leading components of whose activation are interneuronal interaction, the sprouting phenomenon, neurotransmitter connections, neuronal excitability, synaptic mechanisms, etc. [11, 19]. In this aspect, we emphasize that a number of functional disturbances established by us under CBI are, on the one hand, evidence of weakened cerebral resistance and, on the other hand, an impetus for developing a comprehensive pathogenetically oriented correction of the formed disorders aimed at eliminating the developed disturbances and restoring cerebral resistance.

Third, a key position in restoring cerebral resistance under CBI conditions is occupied by the positive effects of separate and combined administration of pentoxifylline, memantine, and Xavron, which made it possible to normalize lost mnestic functions. In this direction of discussion, we should note that we intentionally used the original endonasal route of pentoxifylline administration, which allows faster and more effective contact of high drug concentrations with the brain parenchyma [4, 10]. When endonasal and systemic routes of administration of the applied pharmacological agents were combined, a pronounced neuroprotective effect was obtained, which in some tests was significantly more pronounced than that observed with separate administration of each component of the regimen. Finally, based on the mechanisms of action of pentoxifylline, memantine, and Xavron, together with their marked neuroprotective efficacy, we also conclude that they provide pharmacological support of cerebral resistance after ischemic brain injury.

Fourth, the most effective method of pharmacological correction of cognitive disorders under CBI conditions is combined PF+MEM administration as well as PF+XA administration. The third place in terms of neuroprotective efficacy is occupied by endonasal PF administration. The nootropic efficacy of these treatment regimens was recorded as early as Day 3 of the experiment and persisted until its completion.

We are confident that these data, supported by our previous results, should serve as an experimental basis for the expediency of testing the clinical effects of the indicated drugs with obligatory consideration of the routes of administration.

From a fundamental standpoint, in order to remain methodologically correct, it should be noted that the efficacy of the pharmacological correction scheme we used for mnestic functions more strongly affected learning processes and short-term memory while leaving long-term memory mechanisms relatively aside. To interpret this fact, it is sufficient to point to the different neurophysiological mechanisms of long-term preservation of the memory engram, involving synthesis and maintenance of the metabolism of various protein molecules, processes that are most likely only minimally influenced by the combined PF+MEM or

PF+XA complex. This fact prompts further careful study of mnestic defects in prolonged vascular catastrophes and improvement of pathogenetically substantiated correction schemes for the detected cognitive dysfunctions.

In summary, the nootropic efficacy of separate and combined administration of pentoxifylline, memantine, and Xavron under conditions of chronic brain ischemia enhances cerebral resistance, restores mnestic disturbances manifested by impairment of memory engram formation and retention, and serves as an experimental basis for the expediency of clinical testing of comprehensive pathogenetically substantiated correction of mnestic disorders in a large contingent of patients with chronic ischemia.

Conclusions:

1. Rats with chronic brain ischemia, develop mnestic disturbances, and their severity is time-dependent.
2. The severity of the developed cognitive disorders is characterized by impairment of learning processes and of short- and long-term memory functioning.
3. The positive effects of separate and combined use of pentoxifylline, memantine, and xavron under CBI conditions contributed to restoration of mnestic disturbances.
4. The efficacy of the tested neuroprotection regimens under the experimental conditions was dependent on the duration of the post-ischemic period and on the routes of administration of the pharmacological agents.
5. The most effective method of pharmacological correction of cognitive disorders under CBI conditions is combined PF+MEM administration as well as PF+XA administration. The third place in terms of neuroprotective efficacy is occupied by endonasal PF administration. The nootropic efficacy of these treatment regimens was recorded as early as Day 3 of the experiment and persisted until the end of the experiment.
6. A number of functional disturbances established under CBI conditions constitute evidence of weakened cerebral resistance and an impetus for developing a comprehensive pathogenetically oriented correction of the formed disorders aimed at eliminating the developed disturbances and restoring cerebral resistance.
7. The nootropic efficacy of separate and combined administration of pentoxifylline, memantine and xavron in conditions of chronic brain ischemia enhances cerebral resistance, restores mnestic disturbances manifested by impairment of memory engram formation and retention, and serves as an experimental basis for the expediency of

clinical testing of comprehensive pathogenetically substantiated correction of mnestic disorders in a large contingent of patients with chronic ischemia.

References

1. Kirchev VV, Vastyanov RS. Effect of semax and hopanthenic acid on locomotor activity and neurological deficit in rats under conditions of chronic brain ischemia. Bulletin of Marine Medicine. 2022; 2(95): 109-118. [In Ukrainian].

2. Vastyanov RS, Stoyanov AN, Bakumenko IK. Systemic pathological disintegration in chronic cerebral ischemia. Experimental-clinical aspects. Saarbrucken: LAP Lambert Academic Publishing. 2015: 169 [In Ukrainian].

3. Vastyanov RS, Myronov OO. Correction of pyramidal motor disorders in rats under conditions of chronic brain ischemia due to complex pharmacological correction. Current issues of transport medicine. 2023; 3(73): 200-209. [In Ukrainian].

4. Stoyanov OM, Vastyanov RS, Mirdzhuraev EM, Son AS, Volokhova GO, Kalashnikov VI. Possibilities of intranasal therapeutic influence on the autonomic system in rehabilitation neurology. International Neurological Journal (Ukraine). 2024; 20(3): 156-165. [In Ukrainian]. doi: 10.22141/2224-0713.20.3.2024.1070

5. Chmayssani M, Festa JR, Marshall RS. Chronic ischemia and neurocognition. Neuroimaging Clin N Am. 2007; 17(3): 313-324, viii. doi: 10.1016/j.nic.2007.03.002.

6. Kalaria R, Englund E. Neuropathological features of cerebrovascular diseases. Pathology. 2025; 57(2): 207-219. doi: 10.1016/j.pathol.2024.10.003

7. Kalashnikov VI, Stoyanov AN, Pulyk OR, Bakumenko IK, Skorobrekha VZ. Features of cerebrovascular reactivity in patients of young age with migraine. Wiadomości Lekarskie. 2020; 73(11): 2443-2446

8. Karger G. 30 years of Cerebrovascular Diseases. Cerebrovasc Dis. 2021; 50(1): 1. doi: 10.1159/000514372.

9. Kirchev V.V. Cognitive function restoration in rats with chronic brain ischemia using Semax and hopantenic acid comprehensive administration. Journal of Education, Health and Sport. 2023; 13(4): 404-422.

10. Kirchev VV, Ostapenko IO, Tertyshnyi SV, Buryachkivskyi ES, Vastyanov RS. Neuroprotective effects of deproteinized calf blood haemodialysate in case of intranasally administration under chronic cerebral ischemia. Odessa Medical Journal. 2025; 1(192): 14-19. doi: https://doi.org/10.32782/2226-2008-2025-1-2

11. Moroz VM, Shandra OA, Vastyanov RS, Yoltukhivsky MV, Omelchenko OD. Physiology. Vinnytsia : Nova Knyha, 2016: 722.

12. Prishchepa O.O., Shandra O.A., Vast'yanov R.S. Alterations in Conditioned Food-Procuring Activity Related to Long-Term Pentylenetetrazole Kindling in Rats. Neurophysiology. 2014; 46(5): 452-454

13. Rajeev V, Fann DY, Dinh QN, Kim HA, De Silva TM, Lai MKP. et al. Pathophysiology of blood brain barrier dysfunction during chronic cerebral hypoperfusion in vascular cognitive impairment. Theranostics. 2022; 12(4): 1639-1658. doi: 10.7150/thno.68304.

14. Rost NS, Brodtmann A, Pase MP, van Veluw SJ, Biffi A, Duering M. et al. Post-Stroke Cognitive Impairment and Dementia. Circ Res. 2022; 130(8): 1252-1271.

15. Sanchez-Bezanilla S, Hood RJ, Collins-Praino LE, Turner RJ, Walker FR, Nilsson M. et al. More than motor impairment: A spatiotemporal analysis of cognitive impairment and associated neuropathological changes following cortical photothrombotic stroke. J Cereb Blood Flow Metab. 2021; 41(9): 2439-2455.

16. Stoyanov OM, Vastyanov RS, Myronov OO, Kalashnikov VI, Babienko VV, Hruzevskiy OA. et al. Vegetative system pathogenetic role in chronic brain ischemia, cerebral hemodynamics disorders and autonomous dysregulation. World of Medicine and Biology. 2022; 2(80): 162-168.

17. Stoyanov AN, Mashchenko SS, Kalashnikov VI, Vastyanov RS, Pulyk AR, Andreeva TO, Kolesnik OO. Vestibular dysfunctions in chronic brain ischemia in the post COVID period. Wiadomości Lekarskie. 2023; 76(3): 591-596.

18. Stoyanov OM, Kalashnikov VY, Vastyanov RS, Mirdzhuraev EM, Son AS, Fedorenko TV. et al. Cerebrovascular disorders in patients with COVID-19 consequences pathogenetically determined diagnosis and methods of correction. World of Medicine and Biology. 2024; 2(88); 146-151. doi: 10.26724/2079-8334-2024-2-88-146-151

19. Shandra AA, Godlevsky LS, Vastyanov RS. Epileptic and antiepileptic systems interrelation as the systemic indicator of the complexity of epileptic activity manifestation. Pan-Brain Abnormal Neural Network in Epilepsy. Feng Ru Tang (Ed.). Singapore: Research Signpost; 2009. 99–120

20. Vastyanov RS, Kirchev VV, Muratova TM, Kashchenko OA, Vastyanova OV, Tatarko SV, Zayats LM. Comparative analysis of motor and emotional behavioral disorders in conditions of experimental chronic ischemic and chronic convulsive syndromes. World of medicine and biology. 2021; 2(76): 183-188.

21. Vastyanov RS, Sadovyi OS, Stoyanov OM, Dobrovolskyi VV, Vastyanova OV, Gruzevskyi OA. Cognitive disorders expression and their pathogenetic correction in the dynamics of streptozotocin-induced diabetes. World of medicine and biology. 2021; 4(78): 203-208

22. Su JB, Xi SD, Zhou SY, Zhang X, Jiang SH, Xu B. et al. Microstructural damage pattern of vascular cognitive impairment: a comparison between moyamoya disease and cerebrovascular atherosclerotic disease. Neural Regen Res. 2019; 14(5): 858-867. doi: 10.4103/1673-5374.249234.

23. Zhu T, Wang L, Wang LP, Wan Q. Therapeutic targets of neuroprotection and neurorestoration in ischemic stroke: Applications for natural compounds from medicinal herbs. Biomed Pharmacother. 2022; 148: 112719. doi: 10.1016/j.biopha.2022.112719.

Author's contributions:

Author read and agreed with the publish version of the manuscript.

Funding

This research received no external funding.

Institutional Review Board Statement

Not applicable

Informed Consent Statement

Not applicable

Data Availability Statement

Not applicable

Conflicts of Interest

Author declare no conflict of interest.