Myronov O. O. Peptidergic neurotransmission enforcement restores cerebral resistance in conditions of chronic brain ischemia. Journal of Education, Health and Sport. 2025;83:70617. eISSN 2391-8306. https://dx.doi.org/10.12775/JEHS.2025.83.70617
https://apcz.umk.pl/JEHS/article/view/70617
https://zenodo.org/records/19439804

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;
This article is published with open access at Licensee Open Journal Systems of Nicolaus Copernicus University in Torun, Poland

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 04.07.2025. Revised: 14.07.2025. Accepted: 24.07.2025. Published: 31.07.2025.

UDK 616.8-009.12-008.6-036.12-06

PEPTIDERGIC NEUROTRANSMISSION ENFORCEMENT RESTORES CEREBRAL RESISTANCE IN CONDITIONS OF CHRONIC BRAIN ISCHEMIA

O. O. Myronov

Odesa National Medical University, Odesa, Ukraine

Abstract

The purpose of the study was to determine the efficacy of pentoxifylline, memantine and xavron separate and combined administration in neurological and emotional disorders complex correction in rats in conditions of 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 neurological deficit and emotional behaviour 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 were shown to developed an expressed motor, neurological, and emotional disturbances during the post-ischemic period. Functional recovery occurred gradually within a 7-day observation period, depending on the pharmacological agent and the method of administration. Recovery of impaired functions occurred earlier (from Day 3) and more effectively when pharmacological agents were administered in combination rather than separately. The author shed that the most effective behavioral recovery was observed with combined administration of pentoxifylline

with memantine and pentoxifylline with xavron. Thus, the pharmacological correction strategy targeted key pathogenetic mechanisms of chronic ischemic neuronal injury, including oxidative and ischemic pathways. The results obtained support the feasibility of using pharmacological agents with specialized routes of administration as a pathogenetically justified method of secondary neuroprotection. The author concludes that the efficacy of the developed therapeutic complex indicates the potential for treatment outcomes improvement in patients with cerebrovascular pathology. These results require further clinical verification, particularly regarding intranasal pentoxifylline administration combined with memantine or xavron.

Keywords: cerebrovascular diseases; chronic brain ischemia; cerebral resistance; neurological deficit; emotional behavior; pathogenic mechanisms; pharmacological correction; neuroprotection.

Cerebrovascular diseases (CVD), in fact, pose a significant concern in modern-day neurology, holding prominent places in terms of prevalence, mortality, and disability in almost every region around the globe [6, 7]. Considering the current socio-domestic conditions caused by the full-scale military aggression upon Ukraine, the prevalence of cerebrovascular pathology among the population has increased considerably [11-13].

Over the past ten years, the number of patients with CVD in Ukraine has doubled. This increase is explained both by the growth of slowly progressing chronic forms of cerebrovascular disease and by the rising incidence of stroke [12]. Therefore, the problem acquires considerable medical and social importance, requiring improvement of modern methods of diagnosis, treatment, prevention, and rehabilitation of this group of patients.

According to current concepts, the condition primarily concerns chronic brain ischemia (CBI), whose progressive nature and subclinical manifestations pose a threat to a significant proportion of the population in Europe and worldwide [15, 22]. The pathophysiological mechanisms of CBI are complex and multicascade, involving mutually reinforcing feedback loops and disturbances of neurohumoral regulatory control. As a result, a slowly progressing impairment of cerebral circulation occurs due to the gradual accumulation of ischemic and secondary degenerative changes in the brain. These changes are largely associated with repeated ischemic episodes resulting from atherosclerosis and arterial hypertension and lead to progressive neurological, neuropsychological and mental disorders [3, 10, 14, 16].

Our interest in this issue is related to known data indicating an almost twofold increase in the number of patients with CBI during the last decade, which represents a relatively short time interval for such an unfavorable trend.

In most conditions associated with CBI, the availability of qualified specialists as well as modern diagnostic and therapeutic methods significantly increases the probability of saving patients' lives, although scientific discussions regarding optimal treatment strategies still continue [9, 22]. In view of these problems, the effectiveness of secondary neuroprotection remains particularly relevant, since besides preserving the patient's life, an equally important social aspect is the restoration of neurological functions and recovery from motor and cognitive disorders [10, 13, 14, 16].

Within this context, the concept of "cerebral resistance" is important. This concept reflects the integrated ability of the brain to withstand damaging influences, particularly ischemic disorders. Such resistance results from coordinated regulatory interactions of neurohumoral mechanisms, intracerebral structures, vascular tone, and descending functional influences determined by gray matter structures.

In this regard, maintaining peptidergic neurotransmission appears particularly important given the essential functions of proteins in the brain. Indirect evidence supporting this assumption is provided by the demonstrated neuroprotective effects of peptide-containing compounds, such as Semax, observed in both clinical studies and experimental investigations.

Therefore, we continued a series of experimental studies aimed at evaluating the potential neuroprotective effectiveness of pharmacological compounds of peptide nature under conditions of chronic brain ischemia [4].

The aim of the work was to determine the efficacy of pentoxifylline, memantine and xavron separate and combined administration in neurological and emotional disorders complex correction in rats in conditions of chronic brain ischemia.

Materials and Methods

Animals.

The experiments were conducted in a chronic experimental model on 80 male white rats weighing 180–220 g, maintained under vivarium conditions.

Animal maintenance, handling, and experimental procedures were performed in accordance with:

- the General Ethical Principles of Animal Experiments adopted by the VI National Congress on Bioethics (Kyiv, 2019),
- the European Convention for the Protection of Vertebrate Animals Used for

Experimental and Other Scientific Purposes (Strasbourg, 1985),

- methodological recommendations of the State Pharmacological Center of the Ministry of Health of Ukraine *"Preclinical Studies of Medicinal Products"* (2001),
- and the rules of humane treatment of laboratory animals.

Model of Chronic Brain Ischemia was reproduced by skin incision, isolation, and bilateral ligation of the carotid arteries [3, 9].

Animals randomization.

The animals were divided into the following groups:

1. Control group – intact rats (skin incision only, without carotid artery ligation), *n=9*
2. CBI group – rats with reproduced chronic brain ischemia, *n=16*
3. CBI + Pentoxifylline (PF) – intranasal administration of 10 μl of 2.0% pentoxifylline (Darnitsa, Ukraine), *n=11*
4. CBI + Memantine (MEM) – intraperitoneal administration of memantine; 10 mg/kg (InterChem, Ukraine), *n=11*
5. CBI + Xavron (XA) – intraperitoneal administration of Xavron; 100 mg/kg (Yuria-Pharm, Ukraine), *n=11*
6. CBI + PF+MEM, *n=11*
7. CBI + PF + XA, *n=11*

Animals were observed during 7 days after carotid artery ligation.

Experimental tests used.

During this period the following parameters were evaluated:

- neurological status;
- the expression of neurological deficit using the motor impairment scale [3].

Emotional behavior was studied using two behavioral tests:

1. Response to handling (reaction to an attempt to take the animal in hand) [8].
2. Elevated radial maze test [2].

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 the Severity of Neurological Deficit in Rats with Chronic Brain Ischemia

On Day 1 of the experiment, none of the intact rats in the control group demonstrated weakness of movements, circling ("manege") movements, or motor deficit in the form of paresis or paralysis of the limbs (Table 1). One of the 9 rats showed lethargy and slowed movements. In rats subjected to bilateral carotid artery ligation, a clear neurological deficit was observed, manifested by lethargy and slowing of movements in 14 of 16 rats, weakness and "manege" movements in 16 and 11 animals, respectively, and paresis or paralysis of the limbs in 13 animals. These changes were significant compared with the corresponding indicators in the control group ($p<0.05$).

Comparable changes in motor activity and limb function were also observed in the groups of rats with CBI receiving separate and combined administration of pentoxifylline, memantine, and xavron (in all cases $p<0.05$).

On Day 3 of the experiment, the vast majority of rats with CBI also demonstrated motor deficit and dysfunction of one or several limbs ($p<0.05$ compared with the control group). Our attempts to improve the functional state of animals by separate administration of pentoxifylline, memantine, and xavron were largely unsuccessful. At the same time, it should be noted that only 3 of 10 rats receiving combined PF+MEM administration showed lethargy, slowing, and weakness of movements, which was significantly fewer than in the groups of rats with CBI receiving separate administration of the tested drugs ($p<0.05$). The number of rats demonstrating "manege" movements, as well as paresis or paralysis of the limbs, was also significantly lower ($p<0.05$).

On Day 3 of the experiment, the vast majority of rats with CBI also demonstrated motor deficit and dysfunction of one or several limbs ($p<0.05$ compared with the control group). Our attempts to improve the functional state of animals by separate administration of pentoxifylline, memantine, and xavron were largely unsuccessful. At the same time, it should be noted that only 3 of 10 rats receiving combined PF+MEM administration showed lethargy, slowing, and weakness of movements, which was significantly fewer than in the groups of rats with CBI receiving separate administration of the tested drugs ($p<0.05$). The number of rats demonstrating "manege" movements, as well as paresis or paralysis of the limbs, was also significantly lower ($p<0.05$)

On Day 7 of the experiment, all studied indicators in the groups of rats with CBI receiving separate administration of the tested drugs remained significantly higher than in the control group (in all cases $p<0.05$). In the group with CBI receiving combined PF+MEM administration, only 1 of 10 rats demonstrated weakness of movements and "manege"

Table 1 - Effect of separate and combined administration of pentoxifylline (PF), memantine (MEM), and xavron (XA) on the severity of neurological deficit (%) in rats with chronic brain ischemia

Groups of animals	Lethargy, slowed movements	Weakness of movements	"Manege" movements	Paresis of 1-4 limbs	Paralysis of 1-4 limbs
Day 1					
Group 1 - control, n=9	11	0	0	0	0
Group 2 - CBI, n=16	88*	100*	69*	81*	81*
Group 3 - CBI + PF, n=11	91*	100*	82*	73*	73*
Group 4 - CBI + MEM, n=11	91*	100*	82*	73*	82*
Group 5 - CBI + XA, n=11	91*	100*	73*	73*	82*
Group 6 - CBI + PF+MEM, n=11	82*	91*	82*	82*	82*
Group 7 - CBI + PF + XA, n=11	91*	100*	73*	82*	3*
Day 3					
Group 1 - control, n=9	0	11	0	0	0
Group 2 - CBI, n=13	85*	100*	69*	62*	69*
Group 3 - CBI + PF, n=9	55*	67*	55*	44*	44*
Group 4 - CBI + MEM, n=9	67*	55*	67*	55*	44*
Group 5 - CBI + XA, n=8	75*	88*	75*	50*	50*
Group 6 - CBI + PF+MEM, n=10	30*#@	30##@	20#@	20#@	10##@
Group 7 - CBI + PF + XA, n=8	63*	63*	50*	50*	38*
Day 5					
Group 1 - control, n=9	0	0	0	0	0
Group 2 - CBI, n=12	83*	83*	58*	42*	75*
Group 3 - CBI + PF, n=9	44*	56*	56*	33*	33*#
Group 4 - CBI + MEM, n=9	56*	44*	56*	33*	44*
Group 5 - CBI + XA, n=7	57*	57*	43*	43*	29*#
Group 6 - CBI + PF+MEM, n=10	20#@	10#@	20#@	10#@	0#@
Group 7 - CBI + PF + XA, n=8	25#@	25#@	25#@	13#@	25#
Day 7					
Group 1 - control, n=9	0	11	0	0	0
Group 2 - CBI, n=12	50*	58*	58*	33*	25*
Group 3 - CBI + PF, n=9	22#	22#	11#	0#	11#
Group 4 - CBI + MEM, n=9	33#	33#	22#	22	11#
Group 5 - CBI + XA, n=7	29#	29#	29#	1; 14#	0#
Group 6 - CBI + PF+MEM, n=10	0#	10#	10#	0#	0#
Group 7 - CBI + PF + XA, n=8	13#	0#	0#	0#	0#

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

Notes:

* $p<0.05$ - significant differences compared with the control group of animals;

# $p<0.05$ - significant differences compared with rats with chronic brain ischemia without pharmacological correction;

@ $p<0.05$ - significant differences compared with rats with chronic brain ischemia receiving pentoxifylline and/or memantine

At the same time, in rats with CBI receiving combined PF + XA administration, only one of 8 animals demonstrated lethargy and slowing of movements, while all previously observed signs and symptoms of neurological deficit were absent (in all cases $p<0.05$).

2. Effect of Separate and Combined Administration of Pentoxifylline, Memantine, and Xavron on Emotional Behavior in Rats with Chronic Brain Ischemia

Intact rats throughout the entire observation period avoided the researchers' attempts to take them in hand, vocalized intensely, and attempted to bite the researcher's approaching hand. The mean emotional behavior score ranged from 2.6±0.2 to 3.0±0.3 points (Fig. 1).

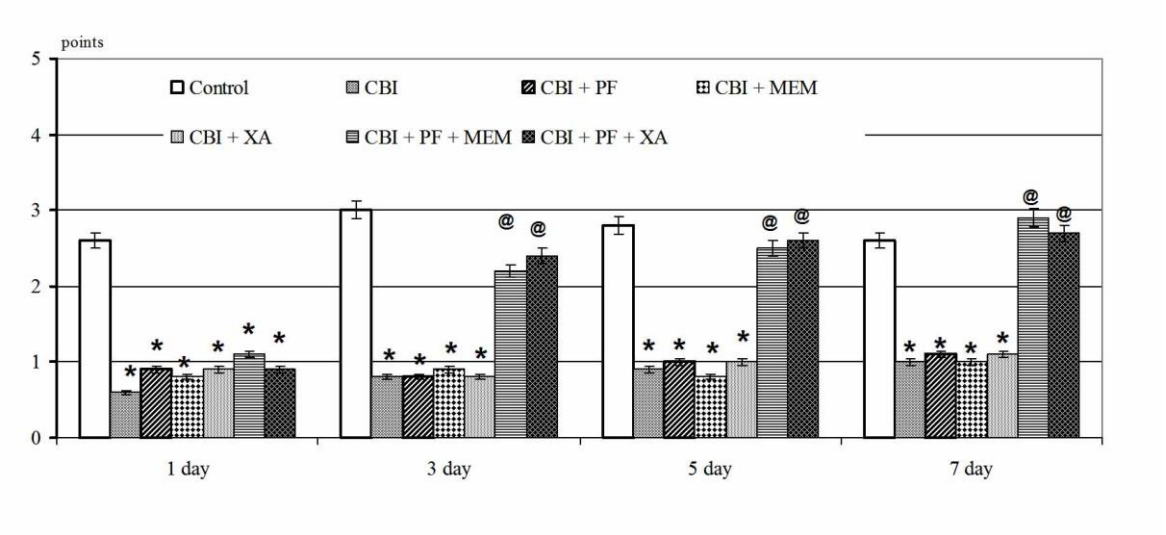

Fig. 1. Effect of separate and combined administration of pentoxifylline, memantine, and xavron on the expression of emotional behavior in rats with chronic brain ischemia

Notes: * - $p<0,05$ - significant differences compared with the corresponding indicators in intact rats;

@ - $p<0,05$ - significant differences compared with rats with chronic brain ischemia receiving pentoxifylline and/or memantine;

Rats with CBI without pharmacological correction, as well as rats with CBI receiving pharmacological agents, were immobilized on Day 1 of the experiment; therefore, the mean indicators of emotional behavior were minimal and significantly lower than the corresponding control values (in all cases $p<0.05$). A clearly minimal absolute severity of the studied parameter was observed in rats with CBI receiving separate administration of the tested drugs during the entire 7-day period of observation, which was comparable to the same indicators in rats with CBI without pharmacological correction.

Starting from Day 3 of the experiment, the mean intensity of the emotional response in rats with CBI receiving combined PF+MEM administration in response to the researcher's

approaching palm was 2.2±0.2 points, which was significantly higher than the corresponding indicator in the groups of rats with CBI receiving separate pentoxifylline and memantine administration ($p<0.05$). At the same time, the value of this indicator in the group of rats with CBI receiving combined PF + XA administration was 2.4±0.2 points, which also showed significant differences compared with the corresponding indicator in the group of rats with CBI receiving separate pentoxifylline and xavron administration ($p<0.05$).

A similar pattern, in which the mean emotional response of rats with CBI receiving combined administration of the tested drugs in response to the researcher's approaching hand exceeded the corresponding indicator in rats with CBI receiving separate administration of pharmacological compounds (in all cases $p<0.05$), was observed until the end of the experiment.

3. Effect of Separate and Combined Administration of Pentoxifylline, Memantine, and Xavron on the Dynamics of Emotional Behavior in Rats with Chronic Brain Ischemia in the Elevated Radial Maze Test

Twenty-four hours after induction of CBI, the majority of rats in all study groups were immobilized, which prevented them from entering the radially arranged arms. Therefore, the studied indicators–the number of arm entries, the time spent in the arms, and the number of entries into the closed arm sections–were substantially lower than the corresponding values in the control group (in all cases $p<0.05$; Table 2). The severe physical condition of the animals, as well as their motor and neurological deficit, caused the rats to remain predominantly in the center of the radial maze and not to visit its closed sections.

On Day 3 of the experiment, the number of entries into the arms and the time spent in the arms in rats with CBI receiving intranasal PF were 2.7-fold and 6.5-fold higher, respectively, than the corresponding indicators in rats with CBI without pharmacological correction ($p<0.05$). A similar pattern of results on Day 3 of the post-ischemic period was obtained in rats receiving combined administration of pentoxifylline with memantine, as well as pentoxifylline with xavron, respectively ($p<0.05$).

On Day 5 of the experiment, the mean number of entries into the arms in rats receiving combined PF+MEM administration was 5.4±0.5, which was 3.8-fold higher than in rats with CBI without treatment and 2.1-fold higher than in rats with CBI receiving intranasal pentoxifylline alone (in all cases $p<0.05$).

Table 2 - Effect of separate and combined administration of pentoxifylline, memantine, and xavron on emotional behavior in the 8-arm elevated radial maze test in rats with chronic brain ischemia

Groups of animals	The investigated indexes		
	Entrances in the maze rays, %	Time spent in the maze rays, %	Number of entries into the maze rays closed areas
Day 1			
Group 1 – control, n=9	9.4±0.8	9.7±0.9	9.2±0.8
Group 2 – CBI, n=16	0.8±0.1*	0.6±0.1*	0*
Group 3 – CBI + PF, n=11	0.9±0.1*	0.5±0.1*	0*
Group 4 – CBI + MEM, n=11	1.2±0.1*	0.7±0.1*	0*
Group 5 – CBI + XA, n=11	1.1±0.1*	0.6±0.1*	0*
Group 6 – CBI + PF+MEM, n=11	0.9±0.1*	0.9±0.1*	0*
Group 7 – CBI + PF + XA, n=11	1.2±0.1*	0.8±0.1*	0.6±0.1*
Day 3			
Group 1 – control, n=9	9.7±0.9	10.4±1.1	9.8±0.9
Group 2 – CBI, n=13	0.9±0.1*	0.7±0.1*	0*
Group 3 – CBI + PF, n=9	2.4±0.2*#	1.6±0.1*#	0.4±0.1*
Group 4 – CBI + MEM, n=9	0.9±0.1*	0.8±0.1*	0*
Group 5 – CBI + XA, n=8	1.1±0.1*	0.7±0.1*	0*
Group 6 – CBI + PF+MEM, n=10	2.2±0.2*#	1.4±0.1*#	0.7±0.1*
Group 7 – CBI + PF + XA, n=8	2.7±0.2*#	1.8±0.2*#	0.6±0.1*
Day 5			
Group 1 – control, n=9	10.7±0.9	12.3±1.2	10.6±0.9
Group 2 – CBI, n=12	1.4±0.1*	0.7±0.1*	0.6±0.1*
Group 3 – CBI + PF, n=9	2.6±0.2*#	1.8±0.1*#	0.9±0.1*
Group 4 – CBI + MEM, n=9	1.7±0.1*	1.1±0.1*	0.6±0.1*
Group 5 – CBI + XA, n=7	1.6±0.1*	1.1±0.1*	0.7±0.1*
Group 6 – CBI + PF+MEM, n=10	5.4±0.5*#@	3.6±0.3*#@	1.9±0.2*#@
Group 7 – CBI + PF + XA, n=8	5.6±0.5*#@	3.1±0.3*#@	1.7±0.1*#@
Day 7			
Group 1 – control, n=9	9.3±0.8	12.6±1.1	10.1±0.9
Group 2 – CBI, n=12	1.7±0.2*	0.9±0.1*	0.6±0.1*
Group 3 – CBI + PF, n=9	3.6±0.3*#	1.9±0.2*#	1.4±0.1*#
Group 4 – CBI + MEM, n=9	2.7±0.2*#	1.8±0.2*#	1.1±0.1*#
Group 5 – CBI + XA, n=7	3.1±0.3*#	2.1±0.2*#	1.2±0.1*#
Group 6 – CBI + PF+MEM, n=10	8.4±0.7#@	4.9±0.4*#@	3.3±0.2*#@
Group 7 – CBI + PF + XA, n=8	7.8±0.6#@	5.2±0.4*#@	3.6±0.3*#@

Notes:

* - $p<0.05$ - significant differences compared with the control group of animals;

- $p<0.05$ - significant differences compared with rats with chronic brain ischemia without pharmacological correction;

@ - $p<0.05$ - significant differences compared with rats with chronic brain ischemia receiving pentoxifylline and/or memantine;

The number of entries into the closed arm sections in rats with CBI receiving combined PF+MEM administration was 1.9±0.2, which also showed significant differences compared with the corresponding indicators in rats with CBI without pharmacological correction and in rats with CBI receiving pentoxifylline alone (in all cases $p<0.05$).

At this stage of the experiment, a similar trend was observed in rats that, after induction of CBI, received pentoxifylline in combination with xavron ($p<0.05$).

Similar changes and comparative differences in the studied radial maze parameters were recorded on Day 7 of the experiment, highlighting the superior effectiveness of combined administration of pentoxifylline with memantine and pentoxifylline with xavron in rats after induction of CBI.

Discussion

Thus, the obtained data indicate that pronounced motor and neurological impairments, as well as disturbances of emotional behavior, are formed in rats during the post-ischemic period. The impaired functions in rats with CBI showed a tendency toward recovery during the 7-day observation period, and the recovery process depended on the type of pharmacological agent, as well as the route and regimen of its administration.

It was clearly demonstrated that impaired functions recovered earlier (starting from Day 3 of observation) and more effectively when the tested drugs were administered in combination compared with the corresponding groups of rats receiving separate administration. The greatest effectiveness according to the behavioral methods used was shown by combined administration of pentoxifylline with memantine and pentoxifylline with xavron. The lowest neuroprotective effectiveness was observed with intranasal administration of pentoxifylline alone. The obtained factual material and its adequate statistical processing demonstrated a more effective normalization of neurological deficit and motor disturbances compared with the recovery of emotional imbalance.

For discussion of the obtained data, we consider it appropriate to focus on the following four points. First, from a methodological point of view, we used the intranasal route for administration of one component of the treatment regimen, namely pentoxifylline. Such a route of pentoxifylline administration, when used separately, promoted early (on Day 3 of the experiment) restoration of emotional behavior in rats with CBI. In general, this route of administration is well known and is advantageous in terms of timing and rapidity of development of the neuroprotective effect [5], given the possibility of faster penetration of the applied drugs into the brain, their contact with ischemically damaged neurons, their

potentially higher concentration in the brain parenchyma, and the absence of the need to cross the blood-brain barrier [1, 3, 5, 8].

Second, in addition to pentoxifylline, two more drugs, namely memantine and xavron, were included in the complex correction of ischemia-induced neurological and emotional disturbances. In this case, considering the mechanisms of neuroprotective action, antioxidant and anti-cytokine effects were implemented through pentoxifylline administration, while NMDA receptor blockade, inhibition of glutamate release, and reduction of glutamate-induced excitotoxicity were achieved through memantine administration; enhancement of antioxidant enzyme activity was associated with xavron administration. Summarizing the above, we would like to emphasize that we adhere to the principle of pathogenetic substantiation of any pharmacological correction regimen, which in this case was achieved through the combined use of pentoxifylline, memantine, and xavron.

Third, treatment regimens similar in composition for cerebrovascular pathology have already been used [6, 7, 9, 22], but we attempted to significantly increase the effectiveness of experimental correction of neurological, motor, and emotional disturbances in CBI by employing the intranasal route of pentoxifylline administration. It should be emphasized that, in this case, the applied pharmacological correction regimen was specifically aimed at affecting the key links in the pathogenesis of chronic ischemic neuronal injury, namely oxidative and ischemic mechanisms of damage, which from a fundamental point of view appropriately completes this stage of the experimental observations.

Finally, we believe that the results of this part of the study demonstrated the effectiveness of restoring peptidergic neurotransmission through the combined action of pentoxifylline with memantine or xavron, which resulted in early normalization of neurological and emotional disturbances under CBI conditions. Peptides use in conditions of cerebral pathology showed their efficacy earlier [3, 8, 17-20]. With regard to the above-mentioned “concept of cerebral resistance” these results highlight the advisability of using such pharmacological agents with specialized routes of administration as a pathogenetically justified method of secondary neuroprotection by interrupting the pathogenetic links of the studied pathological condition and enhancing intracerebral reserves.

Therefore, the demonstrated effectiveness of the developed pathogenetically justified complex for correction of neurological and emotional disturbances during the post-ischemic period indicates the principal possibility of improving treatment efficiency in patients with cerebrovascular pathology through clinical testing of intranasal pentoxifylline administration

and its combined use with memantine or xavron. We consider it appropriate to verify the obtained data in clinical observations in order to formulate final conclusions.

Conclusions:

1. Rats developed an expressed motor, neurological, and emotional disturbances during the post-ischemic period
2. Functional recovery occurred gradually within a 7-day observation period, depending on the pharmacological agent and the method of administration.
3. Recovery of impaired functions occurred earlier (from Day 3) and more effectively when pharmacological agents were administered in combination rather than separately.
4. The most effective behavioral recovery was observed with combined administration of pentoxifylline with memantine and pentoxifylline with xavron.
5. The pharmacological correction strategy targeted key pathogenetic mechanisms of chronic ischemic neuronal injury, including oxidative and ischemic pathways.
6. The obtained results support the feasibility of using pharmacological agents with specialized routes of administration as a pathogenetically justified method of secondary neuroprotection.
7. The efficacy of the developed therapeutic complex indicates the potential for improving treatment outcomes in patients with cerebrovascular pathology. These results require further clinical verification, particularly regarding intranasal pentoxifylline administration combined with memantine or xavron.

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, Kopyova NV. Peculiarities of the emotional behavior of rats in the dynamics of the development of pilocarpine-induced spontaneous seizures. Ukrainian medical almanac. 2009; 12(1): 28–33 [In Ukrainian].
3. 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].

4. 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].

5. 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

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

8. Kirchev VV. Muscle activity and emotional behavior changes in rats with chronic brain ischemia via comprehensive pathogenetic correction. Journal of Education, Health and Sport. 2023; 13(3): 442-457.

9. 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

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

11. Ognev VA, Mishchenko MM, Mishchenko AN, Trehub PO. National trends in morbidity and mortality from circulatory system and cerebrovascular diseases and strokes. Wiad Lek. 2022; 75(5 pt 1): 1152-1155. doi: 10.36740/WLek202205118.

12. Prokopiv MM, Slabkiy GO, Fartushna OY. Prospective analysis of the epidemiology of cerebrovascular disease and stroke among the adult population of Kyiv city, Ukraine. Wiad Lek. 2021; 74(10 cz 2): 2599-2604.

13. 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.

14. 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.

15. 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

16. 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.

17. Shandra AA, Godlevskii LS, Vastyanov RS, Brusentsov AI, Mikhaleva II, Prudchenko IA. et al. Effect of intranigral dosage with delta sleep-inducing peptide and its analogs on movement and convulsive activity in rats. Neurosci. Behav. Physiol. 1996; 26(6): 567-571.

18. Shandra AA, Godlevskii LS, Brusentsov AI, Vastyanov RS, Karlyuga VA, Dzygal AF. et al. Effects of delta-sleep-inducing peptide in cerebral ischemia in rats. Neurosci. Behav. Physiol. 1998; 28(4): 443-446.

19. Shandra AA, Godlevskii LS, Brusentsov AI, Petrashevich VP, Vastyanov RS, Nickel B. et al. Delta-sleep-inducing peptide and its analogs and the serotoninergic system in the development of anticonvulsive influences. Neurosci. Behav. Physiol. 1998; 28(5): 521-526.

20. 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

21. Zhou H, Li J, Zhang C, Huang Y, Jiang H, Chen L. Impact of coffee consumption on mortality in patients with cardiovascular and cerebrovascular diseases: A cohort study. Nutr Metab Cardiovasc Dis. 2025; 35(7): 103855. doi: 10.1016/j.numecd.2025.103855.

22. 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 declares no conflict of interest.