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MOTOR ACTIVITY AND NEUROLOGICAL DEFICIT RESTORATION AS THE RESULT OF COMBINED SEMAX AND HOPANTENIC ACID INFLUENCE IN EXPERIMENTAL CHRONIC BRAIN ISCHEMIA

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Abstract

The prevalence and incidence of cerebrovascular pathology, especially chronic progressive forms, is constantly increasing in modern conditions. Treatment of chronic forms of cerebral blood supply insufficiency is of particular relevance. The insufficient of postischemic disorders efficacy correction and/or behavioral manifestations is justified by the insufficient study of the pathogenetic mechanisms of this complex cerebrovascular catastrophe, which results in insufficiently effective efforts to implement sanogenetic effects. The purpose of the work was the determine the efficacy of Semax and hopantenic acid administration in the treatment of motor disorders and neurological disorders in rats with experimental chronic brain ischemia. Within 7 days, in rats with a model of chronic brain ischemia by bilateral ligation of the carotid arteries, motor activity in the “open field” test and neurological deficit were determined after separate and combined administration of Semax and hopantenic acid. The formation of motor behavior changes and expressed neurological deficit in the dynamics of the post-ischemic period was proved. Semax and hopantenic acid separate and combined

administration contributed to horizontal and vertical locomotor behavior normalization of animals in the “open field” test as well as neurological deficit almost complete elimination. The author believe that the obtained data are an experimental basis for the feasibility of clinical testing of the nootropic effects of Semax and hopantenic acid combined administration in chronic brain ischemia.

Key words: chronic brain ischemia; motor disorders; neurological deficit; semax; hopantenic acid; pathogenetic mechanisms; pharmacological correction

Chronic brain ischemia (CBI) as a phenomenon and pathological process, and, accordingly, such patients represent the vast majority of cases and episodes of cerebrovascular pathology [1, 10]. In this aspect, the treatment of chronic forms of cerebral blood supply insufficiency becomes particularly relevant.

During the formation of cerebral ischemia, and especially in its dynamics, which is a characteristic property of CBI, in experimental and clinical conditions, in addition to the death of the biological organism, a pronounced reduction and/or disorganization of motor and sensory functions is noted [9] with the formation of neurological deficit, which has the character of a pronounced clinical manifestation [10]. The development of spatial orientation, verticalization, coordination, and the work of the motor analyzer, which takes part in these processes, has also been shown in CBI dynamics [1, 6, 8,]. From a fundamental point of view, it is important to imagine that with CBI, regulatory processes in the brain are significantly disrupted, the course of which is provided by vestibular, visual, cutaneous, proprioceptive and other sensory cortical projections and central control [1, 2, 4-6, 10, 11].

The aim of the work is to determine the efficacy of Semax and hopantenic acid administration in the treatment of motor disorders and neurological disorders in rats with experimental chronic brain ischemia.

Material and methods. The experiments were conducted under chronic experimental conditions on Wistar rats, which were kept in vivarium conditions. The maintenance, handling and manipulation of animals were carried out in accordance with the “General Ethical Principles of Animal Experiments” approved by the Fifth National Congress on Bioethics (Kyiv, 2013).

The CBI model was reproduced by skin dissection, isolation and bilateral ligation of the carotid arteries [2]. 5 groups of animals were distinguished: group 1 - control (intact rats, in which only the skin was dissected, n=7). group 2 - experimental (rats with carotid artery ligation and with reproduction of CBI, n=12). Rats of the 3rd group with CBI were injected

with semax (SEM; 0.1%, intranasally, 10μl, n=12). Rats of the 4th group with CBI were injected with hopantenic acid (HA; OOO "|RYK-pharm", 100 mg/kg, i.p., n=12). Rats of the 5th group (n=12) with CBI were simultaneously injected with SEM and HA.

Rats were observed for 7 days after carotid ligation. At the indicated time intervals, rats were tested for motor activity in the open field test for 2 min [3]. Neurological status was assessed using the Motor Shift Assessment Scale [2, 3].

The results were statistically analyzed using the nonparametric Kruskal-Wallis test. The minimum statistical probability was determined at $p<0.05$.

Results

In chronic ischemic syndrome dynamics in rats, the dynamics of a significant reduction in horizontal motor activity indicators in the "open field" test is observed during 7 days of observation ($p<0.01$; Fig. 1).

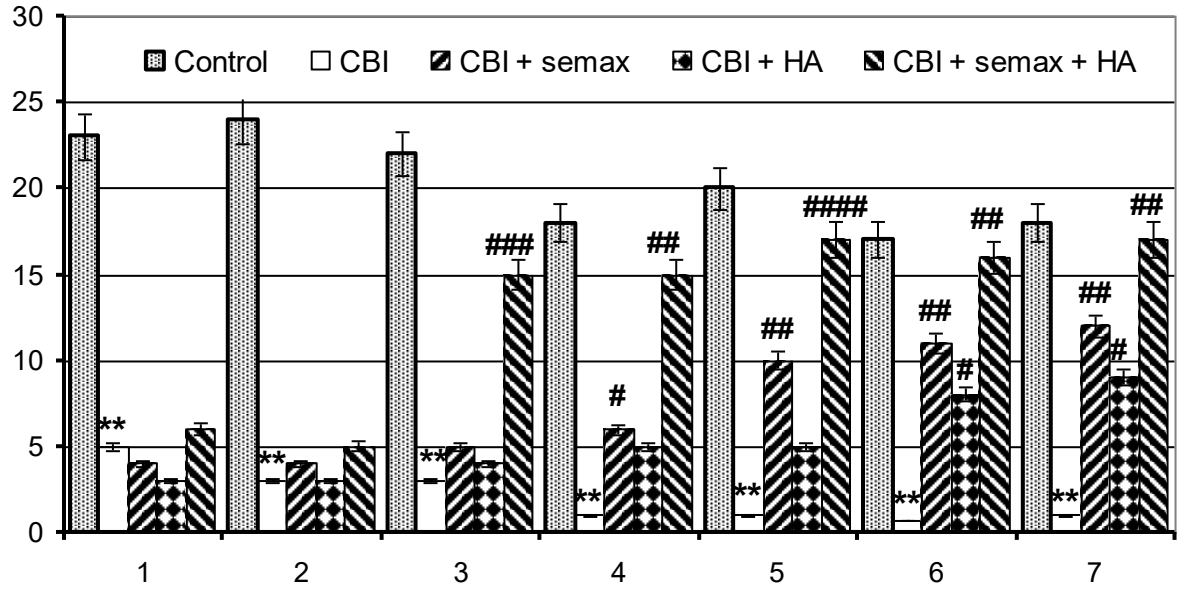

Fig. 1. The effect of separate and combined Semax and hopantenic acid (HA) administration on the horizontal activity indexes in the open field test in rats with CBI

Notes: ** – $p<0.01$ – significant differences of investigated indexes vs the same data in control observations;

- $p<0.05$, ## - $p<0.01$ and ### - $p<0.001$ – significant differences of investigated indexes vs the same data in rats with chronic brain ischemia without pharmacological correction.

On the 3rd day of the postischemic state in the group of rats with CBI, which underwent simultaneous intranasal administration of SEM and HA, the number of crossed squares was 4.7 times higher than in the group of rats with chronic cerebral ischemia without pharmacological correction ($p<0.001$).

Similar dynamics of the studied indicator were recorded until the end of the trial, on the 7th day of the experiment it significantly exceeded the corresponding indicator in the group of rats with CBI without pharmacological correction ($p<0.01$), was comparable with the corresponding indicator in the control observations ($p>0.05$) and significantly exceeded the corresponding indicator in the group of rats with CBI, which were administered HA ($p<0.05$).

Under the specified conditions, the number of crossed squares in the group of rats with CBI which were administered SEM, significantly exceeded the corresponding indicator in the group of rats with CBI without pharmacological correction on the 4th day of the trial ($p<0.05$) with a further increase in the severity of the noted effect. Thus, on the 7th day of CBI the studied index in this group of rats significantly exceeded this index in the group of rats with CBI without pharmacological correction ($p<0.01$) and was comparable to the corresponding control index ($p>0.05$).

Rats with CBI, which were administered HA, crossed an average of 8.7±0.9 squares only on the 6th day of the experiment, which significantly exceeded the corresponding indicator in the group of rats with chronic cerebral ischemia without pharmacological correction ($p<0.05$). The registered effect of HA under the specified conditions was also present on the 7th day of the experiment.

The results of vertical motor activity study in the “open field” test are shown in Fig. 2. The dynamics of a significant reduction in the indicators of vertical motor activity in the “open field” test in the dynamics of CBI during 7 days of observation are traced ($p<0.01$).

We noted a similar expression of SEM and HA effects in rats with CBI when testing their vertical activity in the “open field” test. The maximum activity, which was expressed in the normalization of the number of vertical stands, was noted in the group of rats with CBI, which were simultaneously administered SEM and HA. On the 3rd day of the trial, rats in this group made an average of 3 vertical stands, which was three times higher than the indicator in rats with CBI without treatment ($p<0.001$). The noted effect lasted until the end of the observations.

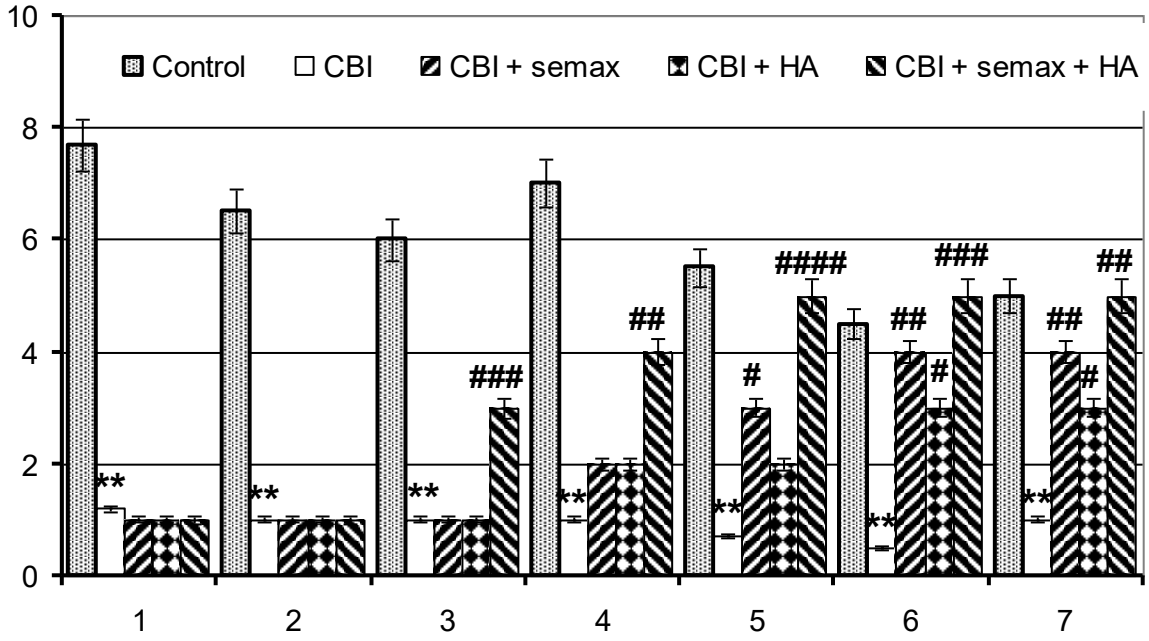

Fig. 2. The effect of separate and combined Semax and hopantenic acid (HA) administration on the vertical activity indexes in the open field test in rats with CBI

Notes: ** – $p<0.01$ – significant differences of investigated indexes vs the same data in control observations;

- $p<0.05$, ## - $p<0.01$ and ### - $p<0.001$ – significant differences of investigated indexes vs the same data in rats with chronic brain ischemia without pharmacological correction.

Minimally expressed activity in terms of normalization of vertical motor indicators in the "open field" test was present in the group of rats that were administered HA during the postischemic period – an expressed effect was achieved on the 6th day of the experiment and lasted until the end of the trial ($p<0.05$, Fig. 2).

When studying the severity of neurological deficit, none of the rats in the control observations demonstrated lethargy, slowness and weakness of movements (only in 1 rat on the 1st, 3rd and 7th days), "manege movements", paresis and paralysis of the limbs (Table 1).

1 day after reproducing ischemia, 10 rats out of 12 demonstrated lethargy and slowness of movements, all rats showed weakness of movements, 7 rats demonstrated "manege movements", which was significantly higher when compared with the corresponding indicators in the control group ($p<0.01$). Similar results without dynamics were recorded throughout the entire observation period.

Table 1

The influence of Semax and HA separate and combined administration on the severity of neurological deficit (%) in rats with chronic brain ischemia

Animal Groups	Lethargy, slowness of movements	Weakness of movements	"Manege" movements	Paresis of 1-4 limbs	Paralysis of 1-4 limbs
1st day					
Control, n=7	0	0	0	0	0
CBI, n=12	83**	100**	58**	83**	17**
CBI +semax, n=12	83**	100**	58**	83**	17**
CBI +HA, n=12	83**	100**	58**	83**	17**
CBI + semax +HA, n=12	67**	83**	67**	83**	9**
3rd day					
Control, n=7	0	14	0	0	0
CBI, n=9	78**	100**	67**	78**	78**
CBI + semax, n=10	60**	80**	60**	60**	20#
CBI + HA, n=9	56*	78**	56*	56*	44*
CBI + semax +HA, n=10	30* # @	40* # @	20 # @	10 ## @	0 ## @@
5th day					
Control, n=7	0	0	0	0	0
CBI, n=8	75**	75**	63**	63**	37**
CBI + Semax, n=9	11##	11##	11##	0##	0##
CBI + HA, n=9	44*	56**	22*	22*	22*
CBI + semax +HA, n=10	20 ## @	20 ## @	10 ## @	0 ## @	0 ## @@
7th day					
Control, n=7	0	14	0	0	0
CBI, n=8	63**	63**	50**	25**	25**
CBI + Semax, n=9	11##	11##	0##	0#	0#
CBI + HA, n=9	22 ##	22 ##	22 #	0#	0#
CBI + semax +HA, n=10	10 ## @	0 ## @	0 ## @	0 ##	0 ##

Notes: * - $p<0.05$ i ** - $p<0.01$ – significant differences of investigated indexes vs the same data in control observations;

- $p<0.05$ i ## - $p<0.01$ – significant differences of investigated indexes vs the same data in rats with chronic brain ischemia without pharmacological correction;

@ - $p<0.05$ i @@ - $p<0.01$ – significant differences of investigated indexes vs the same data in rats with chronic brain ischemia which were administered by semax and/or HA.

Under these conditions, on the 3rd day of the trial, the most expressed effect of neurological disorders normalizing was achieved by rats with CBI, which were administered

SEM and HA together. Thus, lethargy and slowness of movements were recorded only in 3 rats out of 10, which significantly differed from this indicator in rats with CBI without treatment, as well as from similar indicators in rats with CBI, which were administered SEM and HA separately (in all cases $p<0.05$). The remaining indicators also significantly differed from the corresponding data in rats of the specified groups. The noted effect of the treatment complex, which contained SEM and HA, lasted until the end of the experiment.

On the 5th day of the experiment, positive effects in the form of normalization of all neurological disorders (in all cases $p<0.01$) in rats with reproduced CBI were demonstrated by rats that were administered Semax intranasally. This effect was also recorded on the 7th day of the trial.

Normalization of the studied criteria of neurological deficit was achieved the latest, on the 7th day of the experiment, in rats with experiment, which were administered HA for therapeutic purposes.

Discussion

Thus, in rats with a model of CBI, changes in motor behavior are registered already during the 1st day of the trial and neurological disorders develop. Motor disorders were maximally expressed throughout the entire observation period. We consider the established fact of normalization of motor dysfunction and neurological deficit under the influence of the introduction of SEM and HA to be a reliable result of the conducted studies.

From the point of view of CBI treatment, there are the following difficulties: firstly, the course of chronic, i.e. prolonged in the term aspect, brain ischemia itself. Secondly, polypharmacy in treatment and insufficient efficacy of complex correction of symptoms induced by brain ischemia. Thirdly, insufficient efficacy of postischemic disorders correction and/or behavioral manifestations is justified by the pathogenetic mechanisms insufficient research of this complex cerebrovascular catastrophe, which results in insufficiently effective efforts to implement sanogenetic effects [3, 7].

We consider the most effective anti-ischemic scheme for the correction of motor and neurological dysfunctions to be the combined administration of SEM with HA. The next in this series is the intranasal administration of SEM, which was effective from the 3rd day. And the third in the series of anti-ischemic efficacy is the administration of HA, which we registered starting from the 5th day of the experiment. It is worth noting in this aspect that we registered a more pronounced effectiveness of the combined administration of SEM with HA compared to the separate administration of these pharmacological drugs. We emphasize that the restorative effects of the combined administration of SEM and HA were registered earlier

and significantly exceeded the corresponding effects in the case of these two drugs separate administration.

Correct CBI pharmacological correction causing a general neuroprotective effect should also eliminate behavioral disorders under model conditions [12]. Our data have shown that in addition to the general neuroprotective effect, which was expressed in lower mortality of animals with CBI compared to such an indicator in animals with CBI without treatment, separate and combined use of SEM and HA contributed to the normalization of horizontal and vertical locomotor behavior of animals and the complete elimination of neurological deficit.

Conclusions

In rats with a model of chronic brain ischemia, pronounced changes in motor behavior are registered already during the 1st day of the experiment and pronounced neurological disorders develop, which were maximally expressed throughout the entire observation period. Semax and hopantenic acid separate and combined use contributed to both horizontal and vertical locomotor behavior of animals normalization in the “open field” test, as well as the neurological deficit almost complete elimination.

The most expressed neuroprotective effect in rats in conditions of chronic brain ischemia was registered under conditions of Semax and hopantenic acid combined administration. Semax antiischemic efficacy was achieved after intranasal drug administration, which significantly increases the speed of its action on neurons in the event of their probable ischemic damage.

We consider the obtained data to be an experimental basis for the feasibility of clinical testing of the nootropic effects of Semax and hopantenic acid joint administration in chronic brain ischemia.

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Institutional Review Board Statement

The experimental studies were carried out in the conditions of a chronic experiment in accordance with international standards of humane treatment of vertebrate animals and approved by the Ethics Committee of Odesa National Medical University (N7/21, 11 October 2021)

Informed Consent Statement

The data of experimental studies are given. Written informed consent from the patients was not necessary to publish this paper.

Data Availability Statement

The data presented in this study are available on request from the author.