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COMPARATIVE ANALYSIS OF MOTOR AND EMOTIONAL BEHAVIORAL DISORDERS IN CONDITIONS OF EXPERIMENTAL CHRONIC ISCHEMIC AND CHRONIC CONVULSIVE SYNDROMES

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Chronic cerebral ischemia is a phenomenon and pathological process, and, accordingly, patients with chronic cerebral ischemia represent the vast majority of cases and episodes of cerebrovascular pathology. With chronic cerebral ischemia, the 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. The aim of the work is to determine in a comparative aspect the rat's types of motor and emotional behavior disorders in the dynamics of both chronic cerebral ischemia and Kindling-induced chronic convulsive activity. The data obtained indicate that rats with a model of chronic ischemia already during the 1st day of the experiment revealed the expressed changes in motor and postural behavior, muscle and coordination activity, as well as severe neurological and emotional disorders. The obtained results of motor and emotional types of behavior changes in rats under conditions of chronic cerebral ischemia coincided with the results of similar types of behavior testing in rats with picrotoxin kindling. We consider the identity of the registered indexes in conditions of ischemic and convulsive brain damage to be fundamentally important, which testifies the common pathogenetic mechanisms of chronic cerebral ischemia and kindlind-induced chronic convulsive syndrome. The authors believed that a comprehensive pathogenetically based pharmacological correction of motor behavior and emotional sphere will result in anti-ischemic and anticonvulsant effects achievement.

Key words: chronic cerebral ischemia, chronic convulsive syndrome, kindling, motor and emotional behavior disorders, pathogenetic mechanisms, complex pathogenetically based pharmacological correction.

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ПОРІВНЯЛЬНИЙ АНАЛІЗ РОЗЛАДІВ МОТОРНОЇ ТА ЕМОЦІЙНОЇ ПОВЕДІНКИ ЗА УМОВ ВІДТВОРЕННЯ В ЕКСПЕРИМЕНТІ ХРОНІЧНОГО СУДОМНОГО ТА ХРОНІЧНОГО ІШЕМІЧНОГО СИНДРОМІВ

Хронічна ішемія мозку як феномен і патологічний процес, і, відповідно, пацієнти з хронічною ішемією мозку представляють переважну масу випадків і епізодів цереброваскулярної патології. При хронічній ішемії мозку істотно порушуються регуляторні процеси в мозку, перебіг яких забезпечується вестибулярною, зоровою, шкірною, пропріоцептивною і іншими сенсорними кортикальними проекціями і центральним контролем. Мета роботи – визначення в порівняльному аспекті різновидів порушення моторної та емоційної поведінки щурів в динаміці хронічної ішемії мозку та кіндлінг-індукованої хронічної судомної активності. Отримані дані свідчать про те, що у щурів із моделлю хронічної ішемії вже протягом 1-ї доби досліду реєструються виражені зміни моторної та позної поведінки, м'язової та координаційної активності, а також виражені неврологічні порушення та емоційні розлади. Отримані результати зміни моторної та емоційної різновидів поведінки щурів за умов хронічної ішемії мозку співпадали з результатами тестування аналогічних різновидів поведінки у щурів із пікротоксиновим кіндлінгом. Тотожність зареєстрованих показників за умов ішемічного та судомного ураження мозку вважаємо принципово важливим, що свідчить на користь спільних патогенетичних механізмів формування хронічної ішемії мозку та хронічного судомного синдрому за умов кіндлінгу. Вважаємо, що комплексна патогенетично обгрунтована фармакологічна корекція моторної поведінки та емоційної сфери буде також спрямована на формування антиішемічного та протисудомного ефектів.

Ключові слова: хронічна ішемія мозку, хронічний судомний синдром, кіндлінг, порушення моторної та емоційної поведінки, патогенетичні механізми, комплексна патогенетично обгрунтована фармакологічна корекція.

The work is a fragment of the research project "Development of new therapeutic and prophylactic methods and pathogenetic background of their use in inflammatory periodontal diseases together with metabolic syndrome", state registration No. 0120U0021970.

Cerebrovascular pathology has now grown from a medical problem to a social one, because, according to medical statistics, in all countries it is one of the main causes of mortality, disability and the overall decline in the quality of life of patients [4, 10]. In this case, chronic cerebral ischemia is a phenomenon and pathological process, and, accordingly, patients with chronic cerebral ischemia represent the vast majority of cases and episodes of cerebrovascular pathology [8, 13]. In this aspect, the treatment of chronic forms of cerebral insufficiency becomes especially relevant.

There are disappointing data on the steady increase in the incidence of cerebrovascular pathology, the involvement in this pathological process of new contingents of persons, which significantly affects the structure of morbidity [12, 13]. This vascular pathology is difficult to diagnose in the early stages of the disease, in the late – it is very difficult to prescribe effective treatment regimens. The tendency to «rejuvenate»

patients with cerebrovascular pathology is largely associated with socio-economic instability in the country, the presence of extreme conditions, insufficient implementation of the program for the prevention of socially significant diseases such as hypertension, diabetes, cerebral atherosclerosis, etc. [6, 15].

In the formation of cerebral ischemia, and especially in its dynamics, which is a characteristic feature of chronic cerebral ischemia, in experimental and clinical conditions, in addition to the death of the biological organism, there is a pronounced reduction and/or disorganization of motor and sensory functions [2, 4, 6]. We also note the development in the dynamics of chronic cerebral ischemia disorders of spatial orientation, verticalization, coordination, the work of the motor analyzer, which participates in these processes [7, 15]. From a fundamental point of view, it is important to imagine that in chronic cerebral ischemia, the regulatory processes in the brain are significantly disrupted, and their course is provided by vestibular, visual, cutaneous, proprioceptive and other sensory cortical projections and central control [3, 14].

Usually doctors do not pay attention to the above disorders, because the priority is the lives of patients. However, mainly under the conditions of the experiment it was shown that the behavior of rats in chronic cerebral ischemia should be considered in terms of diagnosis, as they may be the earliest signs of impending cerebral catastrophe. Moreover, the correction of the detected behavioral disorders in the conditions of chronic cerebral ischemia will help to improve the functioning of the whole organism and its recovery from ischemic manifestations.

To test the hypothesis regarding the pathogenetic significance of behavioral disorders in the diagnosis and complex pharmacorrection of chronic ischemic syndrome, we performed a series of experimental studies to determine the dynamics of motor and emotional behavior under these conditions. The obtained data were compared with previously known behavioral shifts under the conditions of a Kindling-induced model of chronic epilepsy, the manifestation of which also shows ischemic damage to brain neurons.

The purpose of the study was to determine in a comparative aspect the rat's types of motor and emotional behavior disorders in the dynamics of both chronic cerebral ischemia and Kindling-induced chronic convulsive activity.

Materials and methods. The experiments were performed under a chronic experiment on male Wistar rats weighing 180–250 g, which were fed a standard diet. Rats were provided with free access to food and water; they were kept in standard conditions with a natural 12-hours change of light and darkness, humidity of 60 % and temperature of 22±1° C. The work with laboratory animals was carried out in compliance with generally accepted requirements for laboratory and other experiments with the participation of experimental animals of different species.

The model of chronic cerebral ischemia was reproduced by dissection of the skin, isolation and bilateral ligation with ligatures of the carotid arteries [2]. There were 2 groups of animals: 1 group – control (n=7; intact rats, which had only their skin cut, and ligation of the carotid arteries was not performed) and 2 group – experiment (n=17; rats with ligation of carotid arteries). Rats were observed for 7 days after ligation of the carotid arteries.

To reproduce the chronic convulsive syndrome, a model of chemical kindling was used, which was reproduced by 24-day administration of picrotoxin (PCT; Sigma-Aldrich, Germany) at a subthreshold dose in the range from 0.9 to 1.1 mg/kg. There were 2 groups of rats: 1 group – control (n=6), which was injected with saline solution of sodium chloride. Group 2 – Kindling rats (n=20). Rats were observed for 24 days – this period is necessary for the formation of kindling.

During the above period, motor activity in rats with chronic cerebral ischemia and kindling rats was determined in the "open field" test (Lazarenko NS, 1982) for 2 minutes.

Muscle activity was determined by the time during which rats were able to use the front and rear limbs to hold on to two horizontally spaced sticks [5]. The test for coordination of movements is final in the ability of rats to hold on to a rotating rod (diameter – 25 mm, length – 60 cm, divided by 5 disks into 6 parts). The number of animals that were able to hold on to the rod, which rotates at a speed of 15 revolutions per minute, was determined for 120 seconds. To determine the ability of rats to coordinate movements the "summed grid" test was used.

Neurological status was assessed by calculating the severity of neurological deficit on a scale for assessing motor changes modified by [1].

Additionally, the severity of emotional disorders in the test of aggressive defensive behavior was determined by the nature of the behavioral response of animals to the attempt to take in hand and expressed in points on a scale proposed by R. M. Post et al. (1981). The average severity of aggressive-defensive reactions was taken into account.

The obtained results were calculated statistically using the parametric ANOVA criterion, which was accompanied as a correspondence by the Newman-Keuls test, and the nonparametric Kruskal-Wallis test. The minimum statistical probability was determined at $p<0.05$.

Results of the study and their discussion. The results obtained in this part of the experiments are presented in Fig. 1. The dynamics of significant reduction of indices of horizontal and vertical motor activity in the "open field" test in the dynamics of chronic ischemic syndrome during 7 days of observation ($p<0.01$) is clearly observed. It is also interesting that our comparable indices of white were observed in the group of kindling rats, the dynamics of the formation of chronic convulsive syndrome in which was accompanied by a gradual decrease in the number of crossed squares "open field" (from the 8th day; $p<0.05$) and vertical racks (from the 16th day; $p<0.05$; fig. 1).

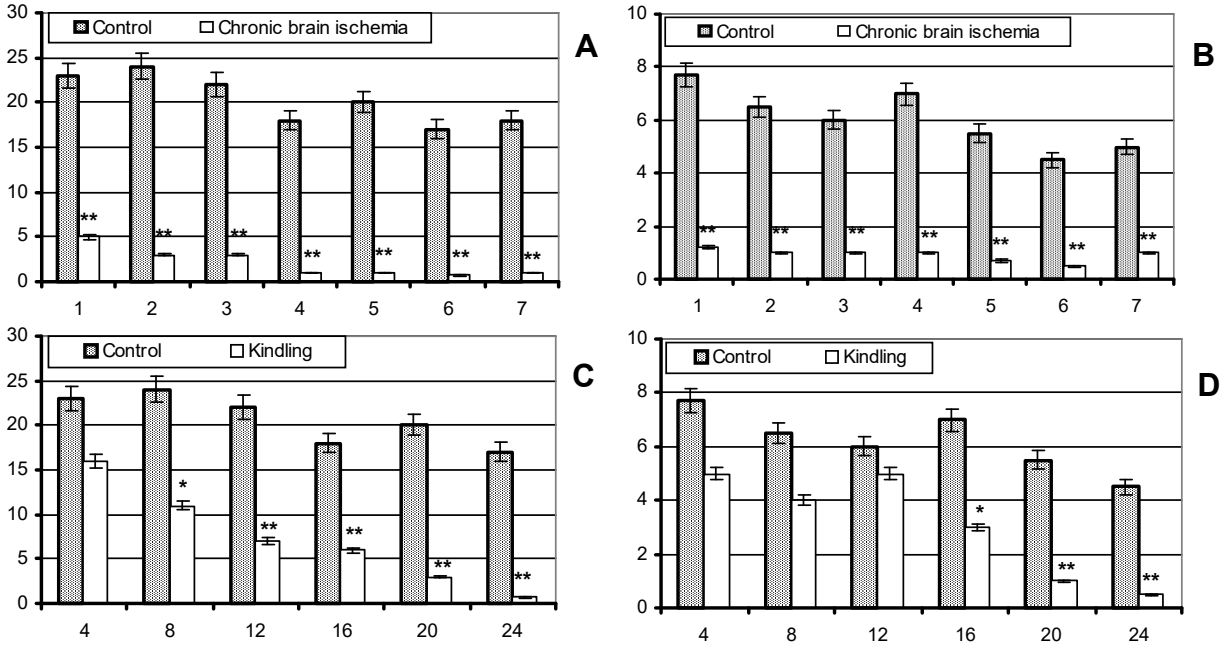

Fig. 1. Comparative characteristics of motor (horizontal – fragments A and C and vertical – fragments B and D) activity of rats with chronic convulsive and chronic ischemic syndrome. Indications: on the abscissa axis – the day of observation (duration of the experiment). On the y-axis: (fragments A and C) – the number of crossed squares in the «open field» test, (fragments B and D) – the number of vertical racks in the «open field» test. * – $p<0.05$, ** – $p<0.01$ – the significant differences of the studied indexes compared with the analogous data in control observations (ANOVA+Newman-Keuls test).

Table 1

Dynamics of neurological deficit (%) in rats with chronic ischemic and chronic convulsive syndrome

Animal groups	Lethargy, slow movements	Weakness of movements	"Manege" movements	Paresis of 1-4 extremities	Paralysis of 1-4 extremities
1st day	Chronic brain ischemia				
Control, n=7	14	0	0	0	0
Ischemia, n=17	88** -2	100**	65** -6	12 (2)	6 (1)
3rd day					
Control, n=7	0	14	0	0	0
Ischemia, n=16	88** -2	100**	63** -6	12	0
5th day					
Control, n=7	14	0	0	0	0
Ischemia, n=15	87** -2	93**	54* -7	13	0
7th day					
Control, n=7	0	14	0	0	0
Ischemia, n=14	93** -1	100**	64 (-5)*	13	0
4th day	Pharmacology Kindling				
Control, n=6	0	17	0	0	0
Kindling, n=20	60* (12)	0	20	0	0
12th day					
Control, n=6	17	0	0	0	0
Kindling, n=20	75** (15)	50**	28* (7)	0	0
20th day					
Control, n=6	0	0	0	0	0
Kindling, n=18	89** (16)	50**	50**	11 (-2)	0
24th day					
Control, n=6	0	0	0	0	0
Kindling, n=17	94** (16)	82** (14)	47** (8)	11 (-2)	0

Indications: The decrease in the number of rats in the groups was due to their death

Notes: * – $p<0.05$ and ** – $p<0.01$– the significant differences of the studied indexes compared with the analogous data in control observations (ANOVA+Newman-Keuls test).

Behaviorally, rats with ischemia also showed constant left and right rotations with an average frequency of 5 to 7 per minute. We found the maximum number of rotations on the 4th day of the experiment – 6.7±0.8, and the number of rotations during the entire observation period did not change significantly. With less pronounced predominantly left-hand rotations, we found in Kindling rats, and their maximum number was in the range from 3 to 4, starting from the 18th day of the experiment.

In the study of the severity of neurological deficits, none of the rats in the control observations did not show lethargy, slowness or weakness of movements (only 1 rat on the 1st, 3rd and 7th day), "manege movements", paresis and paralysis of the limbs (table). One day after the onset of ischemia, 15 rats showed lethargy and slowness of movement, all rats showed weakness of movements, 11 rats showed "manege movements", which was significantly higher compared to the corresponding indices in the control group ($p<0.01$). Similar results without dynamics of increase or decrease were registered during the whole observation period (Table 1).

When determining the neurological deficit in Kindling rats, starting from the 12th day of the experiment, rats began to show movement deficits and mainly left-sided manege movements, these indices in the experimental group significantly exceeded those in the control ($p<0.05$).

Thus, at the time of the formation of kindling, 16 rats out of 17 showed lethargy, slowness of movement, 14 of 17 registered weak movements, 8 rats showed manage movements – these indices significantly exceeded those in the control group of rats.

Kindling rats showed almost the same indices of muscle activity, which for 24 days of observation were unable to stay on horizontally located sticks and on a rotating rod ($p<0.05$; Fig. 2.).

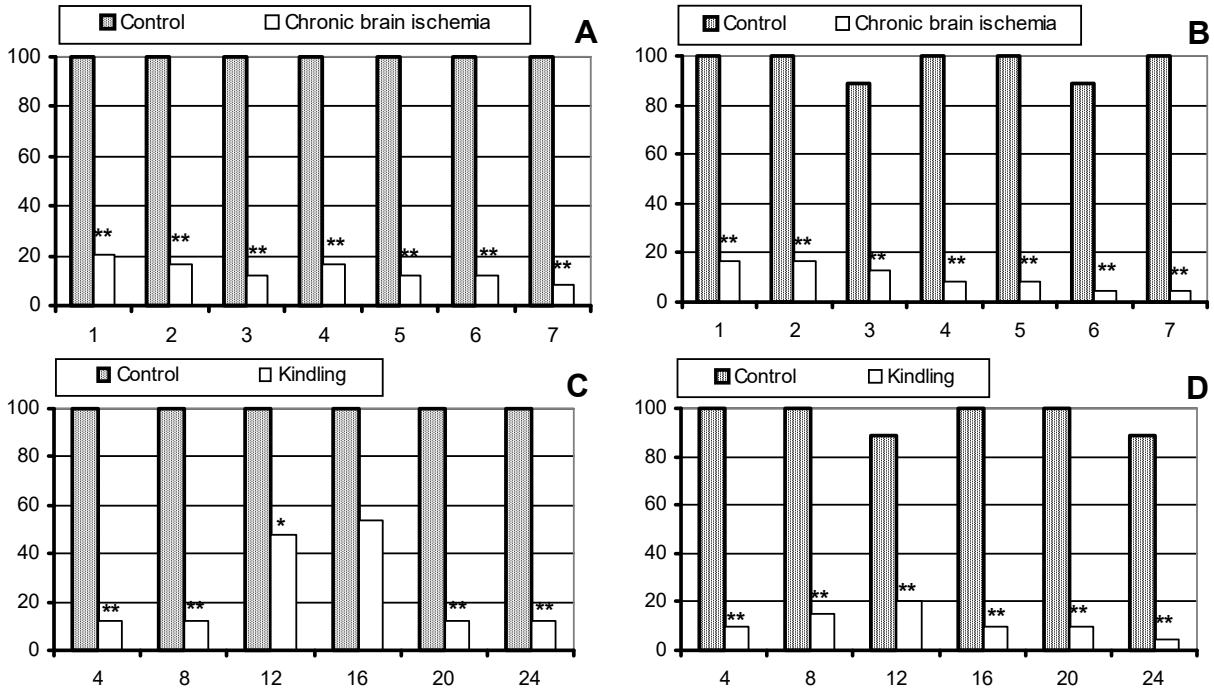

Fig. 2. Comparative characteristics of muscle activity in rats with chronic convulsive and chronic ischemic syndrome. Indications: on the abscissa axis – the day of observation (duration of the experiment). On the y-axis: (fragments A and C) – the number of rats that can be kept on two horizontally arranged sticks, (fragments B and D) – the number of rats that can be kept on a rotating rod (in % in all cases).

All intact rats throughout the observation period were kept on the surface of the metal mesh brought to an angle of 80° (fig. 3, A). Already on the 1st day after bilateral occlusion of the carotid arteries 2 rats out of 17 held on to the surface of the "summed grid", after 2 days – 2 rats out of 16, which was significantly less than the corresponding control indices ($p<0.01$). Similar indices were maintained for 7 days of experiment (fig. 3.).

Kindling rats retained the ability to coordinate activity: only on the 16th day of the experiment, 16 rats out of 19 could not stay on the surface of the 80º metal mesh, which remained like this until the end of the experiment ($p<0.05$, fig. 3. A, B).

All rats of the control group when trying to take in hand tried to hide vocalized (2 rats tried to bite the palm of the researcher) and showed an average expression of emotional behavior in the range from 2 to 3 points. In rats with reproduced cerebral ischemia on the 2nd day of the experiment when trying to pick up the response was more pronounced: only 1-2 rats tried to hide, all the rest tried to bite the palm of the

researcher, i.e. showed maximum emotional behavior, which significantly exceeded the corresponding indices in the control ($p<0.01$, Fig. 3, B).

Testing of emotional behavior in kindling rats showed similar indices, however, the activation of aggressive emotional behavior in Kindling rats occurred at the stage of advanced Kindling and lasted until the 24th day of the experiment ($p<0.05$, fig. 3, D).

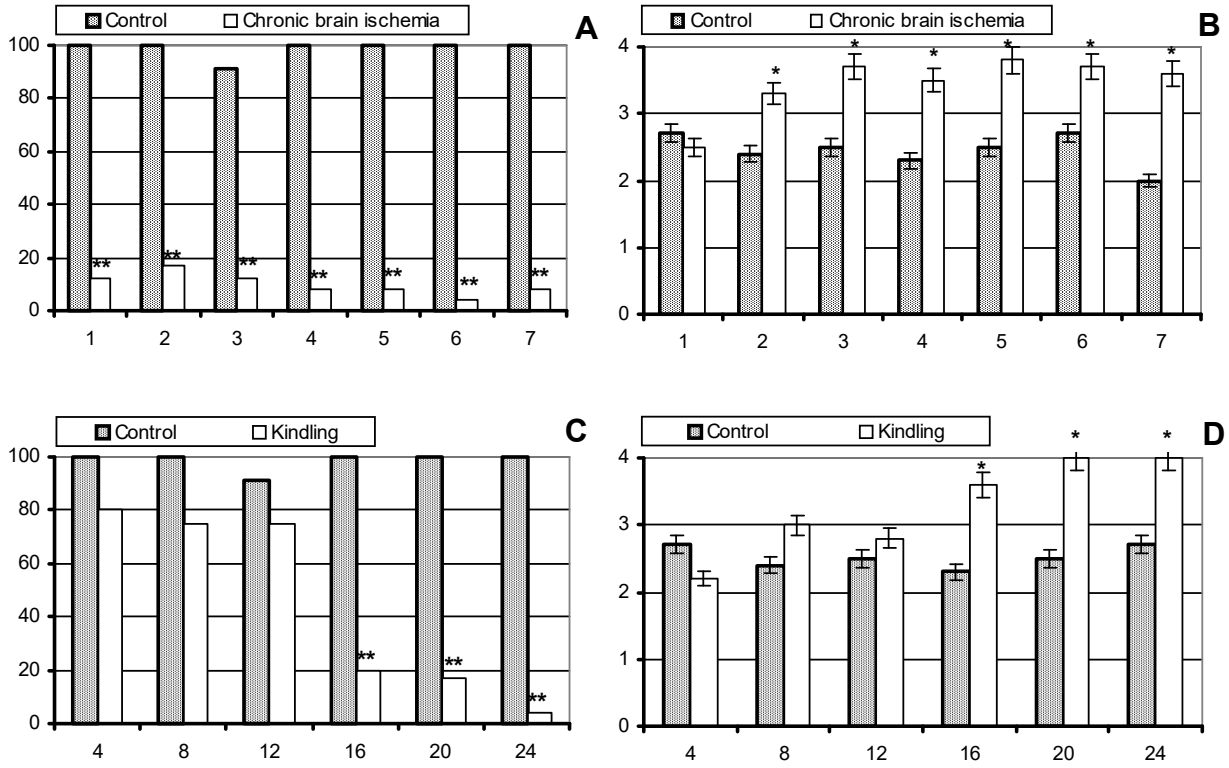

Fig. 3. Comparative indices of coordination activity (fragments A and C) and emotional behavior (fragments B and D) of rats with chronic convulsive and chronic ischemic syndrome. Indications: on the abscissa axis – the day of observation (duration of the experiment). On the y-axis: (fragments A and B) – the number of rats that can stay on the raised grid (in%), (fragments B and D) – the severity of aggressive-protective behavior of rats (points)

Therefore, we note that rats with a reproduced model of chronic ischemia during the 1st day of the experiment registered pronounced changes in motor and late behavior, muscle and coordination activity. Most rats develop severe neurological disorders and emotional disorders. In this context, it is interesting that similar behavioral and emotional disorders are diagnosed in the clinic in patients with ischemic stroke, the clinical manifestations of which are relevant to our model of ischemic brain damage [2].

Interestingly, the detected motor, late, rotational, and muscular, coordination and emotional disorders almost equally maximally expressed throughout the observation period.

Our actual results of changes in motor and emotional behaviors in rats with chronic cerebral ischemia coincided with the results of testing similar behaviors in rats with picrotoxin kindling. Similar results in some way are similar to the ones obtained earlier, but important is the matter of the identicality of the registered actual indices under the conditions of two models of brain damage – ischemic and pharmacological/convulsive. We consider the last fact to be fundamentally important, which testifies in favor of common pathogenetic mechanisms of formation of chronic cerebral ischemia and chronic convulsive syndrome under conditions of kindling. These data are in accordance with the analogous clinical observations [9, 11] and certain experimental trials [5].

Based on the analysis of the results, we consider it appropriate to emphasize the importance and probability of taking into account behavioral disorders and emotional changes in patients as clinical signs of impending ischemic stroke, as well as severe convulsive ictal processes that should develop in the brain.

We are also supporters of the concept regarding the pathogenetic orientation of neuropathological syndromes pharmacological treatment [2], which include behavioral manifestations that were tested in this paper under the conditions of two relevant models. Therefore, given the data obtained, we consider them as an experimental basis for the clinical testing of the effects of pharmacological compounds that can normalize behavioral motor, late and muscular disorders, as well as restore the emotional sphere of patients with chronic cerebral ischemia and/or convulsive syndrome. We are confident that in this case, a complex

pathogenetically sound pharmacological correction of motor behavior and emotional sphere will also be aimed at the formation of anti-ischemic and anticonvulsant effects.

Conclusions

1. In rats with a reproduced model of chronic ischemia already during the 1st day of the experiment, pronounced changes in motor and late behavior, muscle and coordination activity are registered. Most rats develop severe neurological disorders and emotional disorders.

2. The obtained results of changes in motor and emotional types of behavior of rats under the conditions of chronic cerebral ischemia coincided with the results of testing similar types of behavior in rats with picrotoxin kindling.

3. The identicity of the registered indices in the conditions of ischemic and convulsive brain damage is considered fundamentally important, which indicates in favor of common pathogenetic mechanisms of formation of chronic cerebral ischemia and chronic convulsive syndrome in the conditions of kindling.

4. The obtained data are considered as an experimental basis for the feasibility of clinical testing of the effects of pharmacological compounds that can normalize behavioral motor, late and muscular disorders, as well as restore the emotional sphere of patients with chronic cerebral ischemia and/or convulsive syndrome.

Prospects for furthers researches include comprehensive pathogenetically sound pharmacological correction of motor behavior and emotional sphere will be aimed at the formation of anti-ischemic and anticonvulsant effects.

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