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DYNAMIC CHANGES OF STRIATAL NEUROTRANSMITTER SYSTEMS ACTIVITY CAUSE CHANGES IN BEHAVIORAL NON-CONVULSIVE DISORDERS OF DEPRESSIVE NATURE IN THE COURSE OF CHRONIC SEIZURE ACTIVITY FORMATION IN KINDLING MODEL OF EPILEPTOGENESIS

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Abstract

Epilepsy is a chronic neurological disease characterized by recurrent behavioral seizures and affects approximately 1% of the global population. Epilepsy causes recurrent behavioral seizures, which are temporary behavioral changes caused by disordered, synchronized, and rhythmic activations of specific populations of neurons in the brain. Depressive disorders are one of the most common comorbid behavioral disorders in patients with epilepsy, yet they remain undiagnosed and untreated. The aim of the study is to investigate the severity of non-convulsive swimming and emotional behavior and mnemonic processes in rats with a kindling model of epilepsy under conditions of modulation of neurotransmitter systems of the caudate nuclei. It was found that in the dynamics of picrotoxin-induced kindling in rats, impaired swimming behavior, learning and memory abilities, as well as emotional dysfunctions, which are correlates of non-convulsive behavior, are recorded. It

has been proven that the detected disorders of non-convulsive behaviors progressed in the dynamics of the formation of the kindling model of epilepsy and were maximal at the stages of completed kindling and postkindling. The obtained data demonstrate the key role of the striatum in the formation of non-convulsive behavioral disorders. On the 18th day, the pro-convulsive role of striatum is noted, which is confirmed by the enhancement of GABAergic and inhibition of dopaminergic neurotransmission of striatum along with the inhibition of its cholinergic mediation. The completion of the formation of kindling is confirmed by the enhancement of cholinergic and dopaminergic neurotransmission of striatum along with the inhibition of GABAergic mechanisms. In the postkindling stage, activation of cholinergic and dopaminergic neurotransmission of striatum and inhibition of its GABAergic activity are observed. The author considers the data obtained to be an experimental basis for the feasibility of testing clinical diagnostic effects in terms of dynamic monitoring of the behavior of patients with epilepsy during interictal periods, as well as possible corrective pharmacological effects in the case of modulation of the activity of certain neurotransmitter systems and intrastriatal neurotransmission.

Key words: kindling; epileptogenesis; non-convulsive behavior; depression; swimming behavior; learning; memory; emotional behavior; neurotransmitter activity.

Epilepsy is a chronic neurological disease characterized by recurrent behavioral seizures and affects approximately 1% of the global population. The incidence of epilepsy in different countries ranges from 49 to 100 cases per 100,000 people [5] and is somewhat higher in Eastern Europe and developing countries [25]. Epilepsy causes recurrent behavioral seizures, which are temporary behavioral changes caused by disordered, synchronized, and rhythmic activations of specific populations of neurons in the brain that extend to areas associated with primary neuronal circuit damage induced by abnormal neural plasticity [17, 29].

Although involuntary recurrent seizures are a characteristic feature of this chronic disease and can be fatal for patients, experts draw attention to the frequent cases of comorbid epilepsy. It has been proven that patients with epilepsy are at high risk of developing anxiety, depression, learning disorders, and sudden death [14, 16, 28]. To improve the quality of life of patients, it is useful to find out the comorbidity between seizures and other neuropsychiatric disorders.

In this regard, it has been proven that disorders are one of the most common comorbid behavioral disorders in patients with epilepsy, yet they remain undiagnosed and untreated [13, 18, 19, 21, 22]. Clinical observations have shown that depressive disorders predominate in

patients with newly diagnosed epilepsy during the first year of the disease [12]. It has been shown that the prevalence of depression in patients with epilepsy ranges from 11.2 to 60.0% [10, 17], which is significantly higher than in the general population.

From a purely fundamental point of view, epilepsy schematically represents certain temporal relationships between ictal (convulsive) and interictal (nonconvulsive) processes, which are determined by changes in the activity of the epileptogenic pathological system and the antiepileptic system, which initiates sanogenetic effects [1, 9, 27]. Most often, the study of the severity of ictal and interictal processes is performed by recording the electrical activity of neurons located in areas with compromised inhibitory neurotransmission. Along with the registration of electroencephalographic phenomena, one should keep in mind the behavioral seizure correlates of epilepsy [2, 3, 6, 9]. It is important to distinguish and study in a comparative aspect the convulsive behavioral manifestations and nonconvulsive behavioral reactions of patients, which are considered as harbingers of an imminent seizure [7, 8, 11, 15].

Our initial logical premise was that, given the partially comorbid manifestations of depressive behavior in epilepsy, the latter can be considered as manifestations of non-convulsive behavior precisely during interictal time intervals. Therefore, their careful study in behavioral and urgent aspects, elucidation of their neuropathophysiological and neurotransmitter mechanisms is a fundamental point in the diagnostic plan. It is important to understand that the demonstration of behavioral changes during a seizure-free interval is determined by the activity of the antiepileptic system, which in turn is often the result of the enhancement/suppression of the activity of certain brain structures [27]. In this case, as a certain type of behavior is demonstrated or disturbed over a period of time, the seizure/ictal mechanism is increasingly realized.

Thus, a thorough study of non-convulsive behaviors during the interictal periods of chronic epileptogenesis seems to us very important, since in this case, first, a promising mechanism for enhancing the antiepileptogenic effect and possible suppression of the seizure process is found, and, second, the mechanism of impending seizures is investigated.

Clinicians prove that non-convulsive behavioral disorders are recorded in the majority (more than 75%) of patients with epilepsy and are most often the only and leading manifestation of this disease [1, 5]. However, the neuropathogenetic mechanisms of these behavioral disorders remain incompletely studied in the dynamics of chronic epileptogenesis, and the issue of pathogenetically determined correction of non-convulsive epileptiform behavioral disorders is not considered in the aspect of complex treatment of chronic seizure syndrome.

That is why, having certain results of previous studies on the neuropathophysiological mechanisms of non-convulsive behavior in the setting of a kindling-induced model of chronic epileptogenesis [30], we tested our own hypothesis.

The aim of the work is to investigate the severity of non-convulsive swimming and emotional behavior and mnemonic processes in rats with a kindling model of epilepsy under conditions of modulation of neurotransmitter systems of the caudate nuclei.

Materials and methods

The experiments were conducted in a chronic experiment on 112 male Wistar rats weighing 180-250 g, which were kept in vivarium conditions. The animals were kept, treated, and manipulated in accordance with the "General Ethical Principles for Animal Experiments" adopted by the Fifth National Congress on Bioethics (Kyiv, 2013), and guided by the recommendations of the European Convention for the Protection of Vertebrate Animals for Experimental and Other Scientific Purposes (Strasbourg, 1985), the guidelines of the SFC of the Ministry of Health of Ukraine "Preclinical Studies of Drugs" (2001), and the rules for humane treatment of experimental animals.

To reproduce the chronic seizure syndrome, a chemical kindling model was used, which was reproduced by 24-h intraperitoneal injection of picrotoxin (PCT; “Sigma-Aldrich”, Germany; 0.5% solution prepared from powder) dissolved in 0.9% NaCl saline, at a subthreshold dose ranging from 0.9 to 1.1 mg/kg [1].

The rats were randomized as following. Group 1 – control animals (n=9), which were injected with 0.9% saline NaCl solution. Group 2 – kindled rats (in one of the stages of kindling, n=11). Group 3: kindled rats (n=6) with the intrastriatal acetylcholine receptor agonist carbachol injection (CRB; “Sigma-Aldrich”, Germany, 100 ng). Group 4 – kindled rats (n=6) with the acetylcholine receptor antagonist scopolamine intrastriatally (SCO; OJSC “Monpharm”, Ukraine, 500 ng). Group 5 – kindled rats (n=6) with dopaminergic receptor agonist apomorphine intrastriatally (APO; “Sigma-Aldrich”, Germany, 250 ng). Group 6 – kindled rats (n=6) with the dopaminergic receptor antagonist haloperidol intrastriatally (HLP; “Gedeon Richter”, Hungary, 500 ng). Group 7 – kindled rats (n=6) with GABAergic receptor agonist muscimol intrastriatally (MC; “Sigma-Aldrich”, Germany, 2.0 ng). Group 8 – kindled rats (n=6) with the GABAergic receptor antagonist bicuculline intrastriatally (BC; “Sigma-Aldrich, Germany”, 20 ng).

The doses of agonists and antagonists of neurotransmitter systems were chosen according to data give in [9]. The drugs were administered under conditions of free behavior

of animals through previously stereotactically implanted cannulas in the caudate nucleus [23] using a 2.0 μL SGE microinjector (Australia).

The study of non-convulsive behavior of rats was carried out during 3 time intervals: after 18 injections of PCT (stage of developed chronic convulsive syndrome), after 24 injections of PCT (completed pharmacological kindling), after a 14-day interval after the end of kindling formation (38 days of the experiment, postkindling stage) [26]. At the indicated time intervals, the severity of swimming behavior [2, 32], learning and memory processes by forming conditioned reactions of active avoidance (CRA) [5], as well as emotional reactions in the test of aggressive and defensive behavior [3, 24] were determined in rats.

The obtained results were statistically calculated using parametric and nonparametric methods of statistical analysis. To determine the reliability of interval values (the severity of emotional behavior, the number of passive-adaptive acts and the ability to switch to active-adaptive swimming behavior, the number of combinations of a conditional stimulus and an unconditional stimulus necessary for the onset of CRA), we used the parametric ANOVA criterion, accompanied by the Neuman-Keuls test in case of compliance with the reliability criteria. The nonparametric Kruscall-Wallis test was used to determine the reliability of nominal values (indicators of variability and maximum variability). The minimum statistical significance was determined at $p<0.05$.

Results

1. Characteristic of swimming behavior

After placing the rats in a pool of water after the 18th injection of the control group's convulsant, 8 of them recorded one passive-adaptive act of swimming behavior. The average number of passive-adaptive acts in the convulsed rats was 3.27± 0.34, and the value of the variability index was 72%, which was higher than in intact rats ($p<0.05$; Table 1). After swimming, 3 rats climbed up the rope after visual contact with it, the rest – after the rope touched the tip of the muzzle. Thus, the degree of contact with the rope required to exit the pool in the endurance rats after the 18th administration of PCT was 2.1 times greater than in the control ($p<0.05$).

Under similar experimental conditions, the severity of swimming behavior in rats with intrastriatal injection of CRB, HLP and MC was characterized by comparable indicators of the number of passive-adaptive swimming acts with those in kindling rats, while in the case of activation of cholinergic mediation of the striatum, this indicator was 3.72±0.36 and 69.9% higher than the corresponding indicator in control observations ($p<0.05$). In these groups of rats, the indicators of variability and maximum variability also significantly exceeded the

corresponding indicators in intact rats ($p<0.05$). At the same time, the values of maximum variability in these groups of rats significantly exceeded the same values in the kindling rats ($p<0.05$). The ability to switch to active-adaptive swimming behavior in rats with intrastriatal injection of CRB, HLP and MC was difficult, so this indicator was 2.4-3.1 times higher than in the control ($p<0.05$).

Table 1

Characteristic of swimming behavior in rats after the 18th injection of picrotoxin under conditions of modulation of intrastriatal neurotransmitter systems activity

Animal groups	Indicators under study			
	Number of passive-adaptive acts, M±m	Variability index, %.	Maximum variability index, %.	Ability to switch to active-adaptive swimming behavior
1. Control, n=9	2.19±0.27	44	0	0.67±0.06
2. Kindling, n=11	3.27±0.34	72#	0	1.41±0.11
3. Kindling + CRB, n=6	3.72±0.36*	83#	50#[b]	2.07±0.16*
4. Kindling + SCO, n=6	2.43±0.23	33[b]	17	0.53±0.04[a]
5. Kindling + APO, n=6	2.27±0.21	17[b]	0	0.31±0.03[a]
6. Kindling + HLP, n=6	3.58±0.34	67	33#[b]	1.72±0.17*
7. Kindling + MC, n=6	3.64±0.33	83#	33#[b]	1.59±0.13
8. Kindling + BC, n=6	2.36±0.24	33[b]	17	0.49±0.05[a]

Notes (in Tables 1-3): * – $p<0.05$ and ** – $p<0.01$ – significant differences in the studied parameters compared to those in the control group of animals (ANOVA + Newman-Keuls test);

– $p<0.05$ – significant differences in the studied parameters compared to those in the control group of animals (Kruskal-Wallis test);

[a] – $p<0.05$ – significant differences in the studied parameters compared with those in kindling rats (ANOVA + Newman-Kulls test);

[b] – $p<0.05$ – significant differences in the studied parameters compared to those in the kindling rats (Kruskal-Wallis test).

In the groups of rats with intrastriatal administration of SCO, APO and BC, all studied parameters were identical to those of the control groups ($p>0.05$). Moreover, the indicators of variability and ability to switch to active-adaptive swimming behavior in rats of these groups were significantly lower when compared with those in the kindling rats ($p<0.05$).

The study of swimming behavior in rats at the time of completed kindling revealed a significant predominance of the number of passive-adaptive swimming acts, variability and maximum variability indicators in comparison with control data (in all cases $p<0.05$; Table 2). The ability of the kindling rats to switch to active-adaptive swimming behavior was 3.5 times worse than that of intact rats ($p<0.05$).

Table 2

Characteristic of swimming behavior in rats after 24th injection of picrotoxin under conditions of modulation of intrastriatal neurotransmitter systems activity

Animal groups	Indicators under study			
	Number of passive-adaptive acts, M±m	Variability index, %.	Maximum variability index, %.	Ability to switch to active-adaptive swimming behavior
1. Control, n=9	2.37±0.26	44	0	0.81±0.07
2. Kindling, n=11	4.71±0.38*	91#	36#	2.87±0.26
3. Kindling + CRB, n=6	5.33±0.49**	100#	83#	2.76±0.26
4. Kindling + SCO, n=6	2.54±0.23[a]	17[b]	0[b]	0.56±0.06[a]
5. Kindling + APO, n=6	4.93±0.44	83#	83#	3.53±0.32**
6. Kindling + HLP, n=6	2.19±0.19[a]	33[b]	0[b]	0.29±0.04[a]
7. Kindling + MC, n=6	2.32±0.21[a]	33[b]	17	1.00±0.12[a]
8. Kindling + BC, n=6	5.51±0.49**	100#	100#	3.17±0.29**

The same studied parameters of the number of passive-adaptive acts and the ability to switch to active-adaptive swimming behavior, as well as variability and maximum variability, which were significantly higher than in control observations ($p<0.05$) and identical to the corresponding indicators in kindling rats ($p>0.05$), were recorded in groups of animals with intrastriatal injections of CRB, APO and BC.

The opposite results, which were significantly less than in sham-operated rats ($p<0.05$) and comparable to the corresponding control data ($p>0.05$), were recorded in the groups of sham-operated rats with intrastriatal injections of SCO, HLP, and MC.

In rats in the postkindling stage, swimming behavior was characterized by an increase in the number of rats demonstrating the maximum number of passive-adaptive swimming acts, as well as the number of passive-adaptive swimming acts ($p<0.05$; Table 3). The ability to switch to active-adaptive swimming behavior was 2.3 times worse than in the control ($p<0.05$).

Rats in the postkindling stage after injection of CRB, APO, and BC into the striatum also demonstrated all the studied acts of swimming behavior, which were comparable to those of rats with postkindling. However, in the case of intrastriatal microinjections of SCB, HLP, and MC, the variability and maximum variability of the rats were minimal and less than in postkindling rats ($p<0.05$). The number of demonstrated passive-adaptive swimming acts and the ability to switch to active-adaptive swimming behavior in rats of these groups was also less than in rats in the postkindling stage ($p<0.05$).

Table 3

Characteristic of swimming behavior in rats in the postkindling stage under conditions of modulation of intrastriatal neurotransmitter systems activity

Animal groups	Indicators under study			
	Number of passive-adaptive acts, M±m	Variability index, %.	Maximum variability index, %.	Ability to switch to active-adaptive swimming behavior
1. Control, n=9	2.27±0.24	44	0	0.86±0.09
2. Kindling, n=11	3.68±0.29*	64	45#	1.94±0.17*
3. Kindling + CRB, n=6	4.71±0.37*	83#	83	2.51±0.23
4. Kindling + SCO, n=6	2.51±0.23	17[b]	0[b]	0.62±0.06[a]
5. Kindling + APO, n=6	3.91±0.36	67	67	2.94±0.26
6. Kindling + HLP, n=6	2.48±0.22[a]	17[b]	17[b]	0.43±0.04[a]
7. Kindling + MC, n=6	2.29±0.26[a]	0[b]	0[b]	0.57±0.06[a]
8. Kindling + BC, n=6	4.12±0.39*	83#	83	2.67±0.24

2. Characterization of learning and memory processes

The number of combinations of the conditioned stimulus and unconditioned stimulus required for the development of the CRA in rats after the 18th injection of epileptogen was 33% higher than in the group of intact rats ($p<0.05$, Table 4).

Table 4

Characteristic of learning and memory processes in rats after the 18th injection of picrotoxin under conditions of modulation of intrastriatal neurotransmitter systems activity

Animal groups	The number of combinations of conditional stimulus and unconditional stimulus required to generate a CRA		
	Training	Short-term memory	Long-term memory
1. Control, n=9	24.6±2.4	7.1±1.0	2.8±0.4
2. Kindling, n=11	32.8±3.1*	10.6±1.1*	5.5±0.5*
3. Kindling + CRB, n=6	27.2±2.6	8.1±0.8	4.1±0.4*
4. Kindling + SCO, n=6	23.9±2.4[a]	7.8±0.8	2.9±0.3[a]
5. Kindling + APO, n=6	26.1±2.6	9.1±0.8	3.2±0.3[a]
6. Kindling + HLP, n=6	33.3±3.1*	12.3±1.1*	5.8±0.5*
7. Kindling + MC, n=6	34.7±3.3*	11.9±1.2*	6.3±0.5*
8. Kindling + BC, n=6	26.6±2.4	8.4±0.8	3.6±0.3[a]

Notes (in Tables 4-6): * – $p<0.05$ – significant differences in the studied parameters compared to those in the control group of animals (ANOVA + Newman-Keuls test);

[a] – $p<0.05$ – significant differences in the studied parameters compared with those in kindling rats (ANOVA + Newman-Kulls test).

The value of this indicator in 1 day and 7 days after the development of the reflex was 49% and 96% higher than the corresponding control values ($p<0.05$). In sham-operated rats, after intrastriatal injections of HLP and MC, the values were comparable to those in sham-

operated rats ($p>0.05$) and significantly higher than the corresponding control measurements ($p<0.05$). In the case of the introduction of CRB into the striatum of the endling rats, only the number of combinations of the conditional stimulus and the unconditional stimulus necessary for the occurrence of CRA 7 days after its formation significantly exceeded the same indicator in the control group of rats ($p<0.05$).

In the kindled rats after intrastriatal injections of SKO, APO and BC, all the studied parameters were identical to those recorded in the control group. Indicators characterizing the severity of long-term memory were significantly lower in the group of endling rats ($p<0.05$).

All the studied indicators of learning, short- and long-term memory were increased in rats with formed kindling and postkindling ($p<0.05$, Tables 5 and 6). Under these experimental conditions, after the introduction of CRB, APO and BC into the striatum, all the studied parameters were comparable to those in rats with kindling and postkindling ($p>0.05$) and significantly higher than the corresponding control data ($p<0.05$). The opposite results, comparable to those in intact rats, were obtained after intrastriatal microinjections of SCO, HLP and MC. In most cases, the data that were recorded were significantly less than the same data in the kindling rats ($p<0.05$).

Table 5

Characteristic of learning and memory processes in rats after 24 hours of picrotoxin administration under conditions of modulation of intrastriatal neurotransmitter systems activity

Animal groups	The number of combinations of conditional stimulus and unconditional stimulus required to generate a CRA		
	Training	Short-term memory	Long-term memory
1. Control, n=9	24.6±2.4	7.1±1.0	2.8±0.4
2. Kindling, n=11	36.9±3.3**	14.3±1.5**	6.4±0.6**
3. Kindling + CRB, n=6	31.3±2.9	12.6±1.3*	5.3±0.4*
4. Kindling + SCO, n=6	25.6±2.5[a]	8.7±0.7[a]	3.7±0.4[a]
5. Kindling + APO, n=6	35.2±3.4**	14.6±1.6**	6.7±0.6**
6. Kindling + HLP, n=6	27.2±2.4[a]	9.4±0.8	4.6±0.5[a]
7. Kindling + MC, n=6	26.7±2.6[a]	8.9±0.9[a]	5.3±0.6
8. Kindling + BC, n=6	35.7±3.5**	13.7±1.3**	6.1±0.5**

The calculation of the integral index of "preservation" revealed a deterioration of all studied indicators of the cognitive sphere in rats in the dynamics of the formation of kindling (Fig. 1). At the same time, after the 18th injection of PCT, the lowest index (12% less than in the control, $p<0.05$) was noted in rats after the injection of HLP into the striatum. Significantly lower "retention" indices were observed in kindling rats after intrastriatal

injections of CRB and BC ($p<0.05$). A 24% lower "retention" rate compared to the same indicator in intact rats was recorded in post-kindling rats after injection of APO into the striatum ($p<0.05$).

Table 6

Characteristic of learning and memory processes in rats in the postkindling stage under conditions of modulation of intrastriatal neurotransmitter systems activity

Animal groups	The number of combinations of conditional stimulus and unconditional stimulus required to generate a CRA		
	Training	Short-term memory	Long-term memory
1. Control, n=9	24.6±2.4	7.1±1.0	2.8±0.4
2. Kindling, n=11	39.7±3.6**	16.3±1.7*	8.2±0.7**
3. Kindling + CRB, n=6	40.8±4.1**	13.9±1.4*	7.6±0.7**
4. Kindling + SCO, n=6	28.8±2.8[a]	11.3±1.1*[a]	5.3±0.5[a]
5. Kindling + APO, n=6	37.9±3.8*	17.4±1.6*	7.9±0.6**
6. Kindling + HLP, n=6	29.6±2.9	9.9±1.1[a]	5.7±0.6*[a]
7. Kindling + MC, n=6	31.6±3.1	10.3±1.1[a]	6.1±0.6*
8. Kindling + BC, n=6	39.2±3.9**	15.8±1.6*	8.7±0.8**

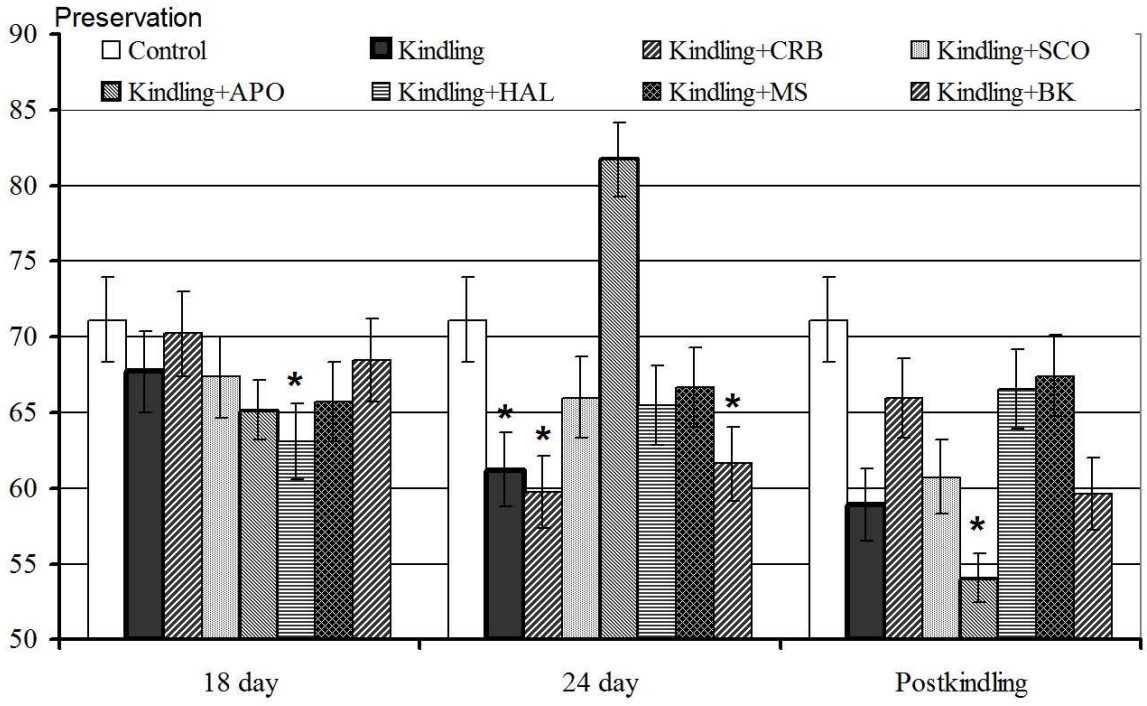

Fig. 1. Changes in the index of "preservation" in kindling rats under conditions of modulation of neurotransmitter systems activity

Notes: * – $p<0.05$ – significant differences in the studied parameters compared to those in the control group of animals;

3. Characteristic of emotional behavior

The severity of emotional behavior in rats during the formation of kindling and in the postkindling stage was constantly increasing, however, the studied indicator did not acquire statistical significance (Fig. 2). The rats tried to avoid the researcher's palm, tried to bite at the first sight of the researcher's hand, and aggressively rushed forward.

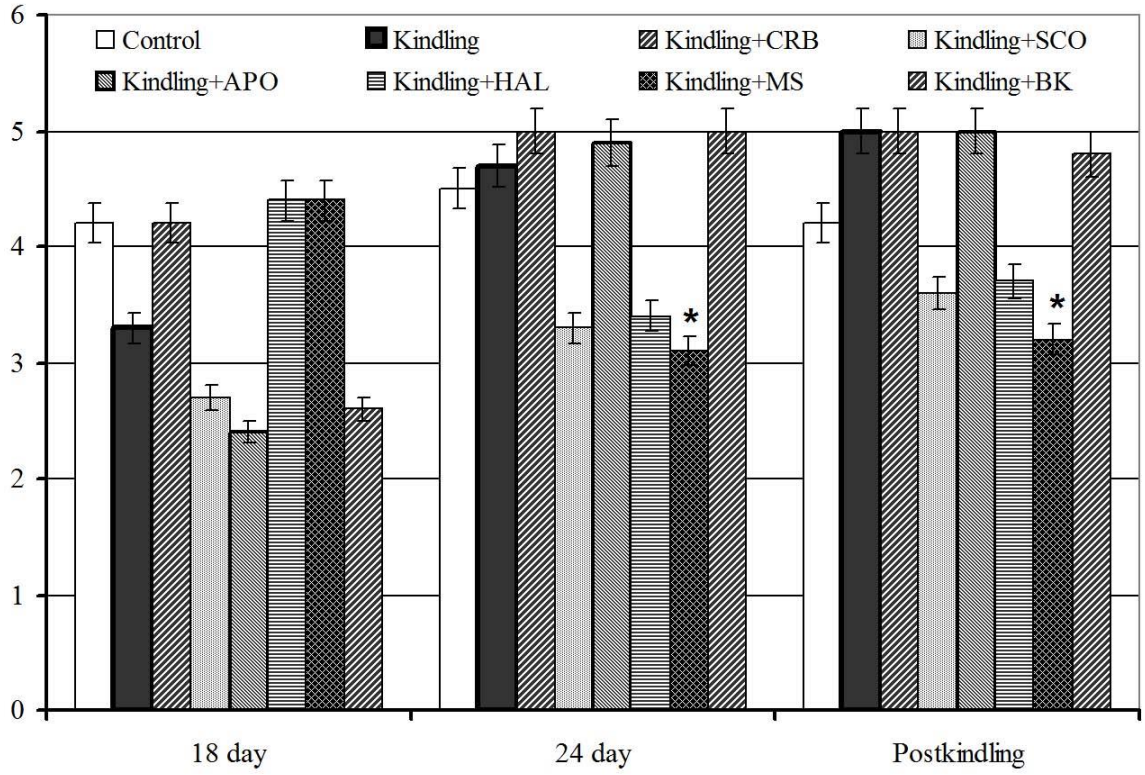

Fig. 2. Changes in emotional behavior in kindling rats under conditions of modulation of neurotransmitter systems activity

Notes: * – $p<0.05$ – significant differences in the studied parameters compared to those in the control group of animals;

After the 18th injection of the convulsant, the maximum indicators of emotional behavior were recorded in rats after intrastriatal injections of CRB, HLP and MC, however, they did not acquire statistical significance. The minimum studied indicators were noted in the groups of rats after the introduction of SCO, APO and BC into the striatum.

In kindling rats, the most pronounced aggressive emotional behavior was noted in the case of intrastriatal injections of CRB, APO and BC. The minimum indicators of emotional behavior were recorded after the administration of SCO and HLP in the striatum. The studied index in the kidding rats after intrastriatal injection of MC was equal to 3.1±0.3, which was 34% less than in the non-kinding rats ($p<0.05$).

We recorded similar dynamics in the severity of emotional behavior in rats at the postkindling stage.

Discussion

Thus, the data obtained indicate the formation in rats of disorders of swimming behavior, learning and memory abilities, as well as emotional dysfunctions in the dynamics of PCT-induced kindling. The forms of behavior selected for the study are correlates of non-convulsive behavior, the disorders of which are characteristic of various models of chronic seizure activity, including the kindling model of epileptogenesis [7-9, 30].

The detected disorders of non-convulsive behavior progressed in the dynamics of the formation of the kindling model of epilepsy and were maximal at the stages of completed kindling and postkindling.

The obtained data demonstrate the fundamental possibility of changing and eliminating behavioral disorders in the case of modulation of intrastriatal neurotransmission. Thus, it can be clearly seen that at the stage of kindling formation, the activation of dopaminergic intrastriatal mediation, together with the inhibition of choline and GABAergic intrastriatal mediation, contributes to the normalization of passive-adaptive forms of swimming behavior and the ability of animals to switch to active-adaptive swimming behavior. That is, swimming behavior at this stage of the formation of the kindling model of epilepsy is determined by the activation of the choline and GABAergic neurotransmitter systems of the caudate nucleus and the suppression of its dopaminergic mediation.

At the stage of completed kindling, as well as at the stage of increased seizure readiness – postkindling – the swimming behavior of rats is determined by the activation of choline and dopaminergic intrastriatal neurotransmission along with the inhibition of GABAergic mediation. It should be noted that the data obtained demonstrate striatal hyperactivation in the dynamics of the formation of killing-induced chronic epileptogenesis and are consistent with the data obtained in the study of other types of non-convulsive behavior in killing and other chronic forms of seizure activity [2, 4, 30].

Mnemonic functions in kindling are also characterized by a deterioration in the learning and functioning of short-term memory and the preservation of its engram in long-term memory. At the stage of formation of chronic seizure activity, cognitive processes are determined by the activation of intrastriatal choline and GABAergic transmission and suppression of dopaminergic activity. At the stage of completed kindling and post-kindling, mnemonic disorders persist after activation of choline and dopaminergic neurotransmission and corresponding inhibition of the GABAergic system. It is clear that oppositely directed

activity and its promising modulation is a way to correct cognitive disorders in established and resistant to anticonvulsant drugs epileptic activity.

The study of the integral indicator of "preservation" in the dynamics of the formation of killing-induced seizure activity has shown that the most pronounced mechanism of mnemonic dysfunctions at the stage of killing formation is the blocking of dopamine transmission of striatum, at the stage of killing – activation of cholinergic and blocking of GABAergic transmission of striatum, at the stage of postkindling – activation of dopaminergic neurotransmission. Taking into account the proven catecholaminergic mechanisms of learning and memory processes, on the one hand, and the complex mechanisms of intrastriatal relay neurotransmission, the ways of realization of nootropic effects in the case of chronic seizure activity with a certain correction of the mediator functions of the caudate nucleus are clearly expressed.

According to the fundamental data, the functioning of mnemonic processes and the successful formation of the memory engram have a direct correlation with the emotional background, which often acts as a reinforcement of the conditioned reflex mechanism of memory [20]. The data we obtained on the severity of emotional behavior, its disruption in the dynamics of the formation of kindling-induced chronic seizure activity and neurotransmitter mechanisms clearly correlate with similar data on the studied aspects of mnemonic dysfunctions under model conditions and also highlight promising areas for testing corrective and/or restorative effects in the clinic.

When discussing this part of the results, we note the pro-convulsant role of the striatum at the time of the formation of the kindling, i.e., on the 18th day of the convulsant administration, which is confirmed by the enhancement of GABAergic and inhibition of the activity of dopaminergic neurotransmission of the striatum along with the inhibition of its cholinergic mediation. Completion of the formation of the kindling is considered to be the point of equilibrium, when the activity of the antiepileptic system increases, and this is also confirmed by changes in the activity of the caudate nucleus by increasing its cholinergic and dopaminergic neurotransmission along with inhibition of GABAergic mechanisms. In the postkindling stage, at the end of the convulsion-free period, during which the activity of the pathological epileptic system becomes maximally pronounced, hyperactivation of opioid mechanisms is noted in the structure of non-convulsive behavioral disorders. At this point, choline and dopaminergic neurotransmission of the striatum is activated and its GABAergic activity is suppressed [31].

We consider the obtained data to be a proof of the functional interaction of the convulsive epileptogenic and antiepileptogenic systems in the dynamics of the formation of kindling-induced chronic seizure activity [5, 27]. We see the prospect of the results obtained in the proven effects of leveling behavioral disorders in the case of activation or blockade of intrastriatal neurotransmission in specific intervals of chronic epileptogenesis. Our evidence suggests the feasibility of testing clinical diagnostic effects in terms of dynamic monitoring of the behavior of patients with epilepsy during interictal periods, as well as possible corrective pharmacological effects in the case of modulation of the activity of certain neurotransmitter systems and intrastriatal neurotransmission.

Conclusions:

1. In rats, in the dynamics of picrotoxin-induced kindling, impaired swimming behavior, learning and memory abilities, as well as emotional dysfunctions, which are correlates of non-convulsive behavior, are recorded.

2. The detected disorders of non-convulsive behavior progressed in the dynamics of the formation of the kindling model of epilepsy and were maximal at the stages of completed kindling and postkindling.

3. At the stage of formation of kindling, swimming behavior is determined by the activation of choline and GABAergic neurotransmitter systems of the caudate nucleus and the inhibition of its dopaminergic mediation. At the stage of completed kindling, as well as at the stage of post-kindling, the swimming behavior of rats is determined by the activation of choline and dopaminergic intrastriatal neurotransmission along with the inhibition of GABAergic mediation.

4. Mnemonic functions in kindling are characterized by a deterioration in the process of learning and functioning of short-term memory and the preservation of its engram in long-term memory. At the stage of formation of chronic seizure activity, cognitive processes are determined by the activation of intrastriatal choline and GABAergic transmission and suppression of dopaminergic activity. At the stage of completed seizure and post-seizure, mnemonic disorders persist after activation of choline and dopaminergic neurotransmission and corresponding inhibition of the GABAergic system.

5. The most pronounced mechanism of mnemonic dysfunctions at the stage of formation of kindling is blocking of dopamine transmission of striatum, at the stage of kindling – activation of cholinergic and blocking of GABAergic transmission of striatum, at the stage of postkindling – activation of dopaminergic neurotransmission.

6. The data obtained demonstrate the key role of striatum in the formation of non-convulsive behavioral disorders. On the 18th day, the pro-convulsive role of striatum is noted, which is confirmed by the enhancement of GABAergic and inhibition of dopaminergic neurotransmission of striatum along with the inhibition of its cholinergic mediation. The completion of the formation of kindling is confirmed by the enhancement of cholinergic and dopaminergic neurotransmission of striatum along with the inhibition of GABAergic mechanisms. In the postkindling stage, activation of cholinergic and dopaminergic neurotransmission of striatum and inhibition of its GABAergic activity are observed.

7. Our findings suggest the feasibility of testing clinical diagnostic effects in terms of dynamic monitoring of the behavior of patients with epilepsy during interictal periods, as well as possible corrective pharmacological effects in the case of modulation of the activity of certain neurotransmitter systems and intrastriatal neurotransmission.

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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.

Conflicts of Interest

There is no conflict of interest.