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Стаття надійшла 16.01.2020 р.

DOI 10.26724/2079-8334-2021-1-75-181-186
UDC 616.8-009.12-008.6-036.12-06:616.89-008.454]-092

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PATHOGENETIC MECHANISMS OF CONVULSIVE DEPRESSIVE SYNDROME IN THE CONDITIONS OF KINDLING-INDUCED MODEL OF EPILEPTOGENESIS

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Non-convulsive behavioral disorders are registered in the majority (over 75 %) of patients with epilepsy and are most often the only and most prominent manifestation of this disease. However, the neuropathogenetic mechanisms of these behavioral disorders remain insufficiently studied in the dynamics of chronic epileptogenesis, and the question of pathogenetically determined correction of non-convulsive epileptiform behavioral disorders is not considered in terms of comprehensive treatment of the chronic convulsive syndrome. The purpose of our work was to study the dynamics of the postural behavior severity in rats under the conditions of different periods of formation of picrotoxin-induced kindling using the striatal functional activity modulation. The obtained data indicate the hyperactivation of the striatum under the conditions of the development of picrotoxin-induced chronic convulsive activity, which functional activity depends on the term of the convulsive syndrome manifestation. The study of non-convulsive types of motor, emotional, swimming, cognitive behavior and their disorders during the specified time intervals of the formation of chronic epileptic activity is important for the use of certain behavioral disorders as an early diagnosis of epilepsy when the motor seizure disorders are absent and the probable behavior disorders do not reach maximum intensity

Key words: kindling, postkindling, picrotoxin, non-convulsive behavioral disorders, postural behaviour, striatum, striatal neurotransmitter systems.

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ПАТОГЕНЕТИЧНІ МЕХАНІЗМИ СУДОМНОГО ДЕПРЕСИВНОГО СИНДРОМУ ЗА УМОВ КІНДЛІНГ-СПРИЧИНЕНОЇ МОДЕЛІ ЕПІЛЕПТОГЕНЕЗУ

Несудомні порушення поведінки реєструються у більшості хворих на епілепсію і є, частіше за все, єдиним та провідним проявом вказаного захворювання. Проте, нейропатогенетичні механізми вказаних розладів поведінки залишаються неостаточно дослідженими в динаміці формування хронічного епілептогенезу, а питання стосовно патогенетично обумовленої корекції несудомних епілептиформних розладів поведінки не розглядається в аспекті комплексного лікування хронічного судомного синдрому. Метою нашої роботи було дослідження динаміки вираженості позно-тонічної поведінки щурів за умов різних періодів формування пікротоксин-індукованого кіндлінга при модуляції функціональної активності хвостатих ядер. Йдеться про гіперактивацію стріатуму за умов розвитку пікротоксин-індукованої хронічної судомної активності, функціональна активність якого залежить від терміну маніфестації судомного синдрому. Дослідження безсудомних різновидів моторної, емоціональної, плавальної, когнітивної поведінки та їх розладів протягом відзначених термінових інтервалів формування хронічної епілептичної активності є важливим для застосування визначених порушень поведінкової активності в якості ранішньої діагностиці маніфестації епілепсії, коли моторні судомні прояви відсутні, а ймовірні поведінкові розлади не набувають максимальної інтенсивності.

Ключові слова: кіндлінг, посткіндлінг, пікротоксин, несудомні порушення поведінки, позно-тонічна поведінка, стріатум, нейромедіаторні системи стриатуму.

The work is 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.

Non-convulsive behavioral disorders are registered in the majority (over 75 %) of patients with epilepsy and are most often the only and most prominent manifestation of this disease [1, 4]. However, the neuropathogenetic mechanisms of these behavioral disorders remain insufficiently studied in the dynamics of chronic epileptogenesis, and the question of pathogenetically determined correction of non-convulsive epileptiform behavioral disorders is not considered in terms of comprehensive treatment of the chronic

convulsive syndrome. There are some explanations for this formulation of the problem, one of which is the lack of adequate models of epileptogenesis, which would be able to clarify the peculiarities of the behavioral disorders formation in the dynamics of formation and excessive spread of chronic convulsive activity. Another explanation is the polymorphism of the disease: in chronic epilepsy, in addition to a significant number of episodes of behavioral disorders associated with the underlying disease, the development of numerous complications, the likelihood of *status epilepticus*, involuntary delayed seizures, frequent development of drug-resistant forms of the disease, etc. [5, 6].

Since the model of pharmacological kindling of epileptogenesis is being determined as the adequate one [3, 10], this makes it possible to trace the dynamics of the formation of epileptic activity of behavioral disorders and determine the imbalance of activity of the epileptic and antiepileptic systems, taking into account the data obtained by Academician G.M. Kryzhanovsky and his students. The comprehensive study of the second aspect mentioned above is more difficult, given the mutual strengthening of convulsive and non-convulsive (behavioral) disorders in the formation of chronic epileptic activity. The latter is confirmed by the fact that frequent and severe episodes of psychological stress are risk factors for convulsive disorders and provoke the development of epilepsy [8, 10], which significantly increases seizures intensity and their frequency in patients with epilepsy. Under such conditions, convulsive reactions can be minimized by psychiatric anti-stress treatment [6].

The study of postural behavior peculiarities permits a comprehensive assessment of minimal behavioral disorders and provide an idea of the prevalence of individual neurotransmitter systems' activity [8]. With this in mind, we investigated the structure of postural-tonic syndrome in the dynamics of kindling-induced convulsive activity. Given the determination by the caudate nucleus of the formation of convulsive activity and behavioral disorders under the conditions of pharmacological kindling, it was also interesting to study the severity of postural behavior under the conditions of changes in the functional state of the striatum made by the intrastriatal (i/str) introduction of agonists and antagonists of the leading neurotransmitter systems of the striapalidar system.

The purpose of the work was to study the dynamics of the severity of postural behavior in rats under the conditions of different periods of the formation of picrotoxin (PCT)-induced kindling using the striatal functional activity modulation.

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

In order 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 [3].

The following groups of rats were isolated. Group 1 – control animals (n=6), which were injected with normal saline. Group 2 – Kindling rats (n=9), in which Kindling was reproduced via daily intravenous administration of picrotoxin (PCT; Sigma-Aldrich, Germany; 0.5 % solution was prepared from the powder) dissolved in the normal saline dose of 0.9–1.1 mg/kg. Group 3 – rats with PCT-induced kindling (n=6), which were injected with carbachol – an agonist of acetylcholine receptors (CRB; "Carbacholin", "Chemical-Pharmaceutical Association", Russia, 100 ng). Group 4 – rats with PCT-induced kindling (n=6), which were injected intravenously with scopolamine – an antagonist of acetylcholine receptors (SKO; JSC "Monpharm", Ukraine, 500 ng). Group 5 – rats with PCT-induced kindling (n=6), which were injected intravenously with apomorphine – an agonist of dopaminergic receptors (APO; "Sigma-Aldrich", Germany, 250 ng). Group 6 – rats with PCT-induced kindling (n=6), which were injected intravenously with haloperidol – a dopaminergic receptor antagonist (GLP; Gedeon Richter, Hungary, 500 ng). Group 7 – rats with PCT-induced kindling (n=6), which were injected with muscimol – an agonist of GABAergic receptors (MSC; "Sigma-Aldrich", Germany, 2.0 ng). Group 8 – rats with PCT-induced kindling (n=6), which were injected intravenously with bicukulin – an antagonist of GABAergic receptors (BC; "Sigma-Aldrich", Germany, 20 ng). Doses of used neurotransmitter systems agonists and antagonists were chosen according to our previous works [2]. The drugs were administered under the conditions of the free behavior of animals through previously stereotactically implanted cannulas in the caudate nucleus [7] using the SGE microinjector (Australia) with a volume of 2.0 μl.

The severity of postural behavior in rats was noted in the dynamics of PCT-induced kindling three times: (a) During the period of formation of kindling – in response to the 18th injection of an epileptogen;

(b) Immediately after the end of reproduction of kindling – 1 day after the last (24th) injection of PCT; (c) By the end of the so-called post-kindling, 12 days after the last PCT administration.

In these three episodes of kindling formation, rats' behavioral responses were evaluated according to the method described in [8].

In order to study the neuropathophysiological mechanisms of behavioral disorders, the rats were i.p. given the opiate receptor blocker naloxone ("Dupont", USA, 1 mg/kg), the non-competitive antagonist of glutamate/aspartate receptors ketamine ("Callipsol", Gedeon Richter, 5 mg/kg), and the M-choline blocker atropine ("Sigma-Aldrich", Germany, 1 mg/kg).

The data obtained calculated statistically using the ANOVA parametric criterion, which was accompanied by the Newman-Kulls test. $p<0.05$ was determined as the minimal statistical probability

Results of the study and their discussion. Postural behavior of rats after the 18th convulsant injection.

In response to the 18th administration of PCT in the dynamics of the formation of the Kindling epileptogenesis, the postural behavior of rats was characterized by the fact that when they were placed in the center of the horizontal platform, the forelimbs were spread (5 rats out of 9). When thrown to the side, 8 out of 9 animals remained in an awkward position for more than 1 minute. Exophthalmos was reported in most rats (8 out of 9). After the cornea was touched with a brush, the corneal reflex was absent in most animals. The hind limbs were abducted in 8 of 9 rats. The average pain severity due to the tail pinching was 1.14±0.06 points, which was by 2.5 times less than in the control observations ($p<0.05$).

The postural behavior of rats with activation and blockade of striatal cholinergic receptors did not differ significantly between the two groups and was comparable to the one shown by intact rats in control observations.

In 4 out of 6 rats, in the case of intrastriatal apomorphine administration after being placed in the center of the horizontal platform, the forelimbs were spread. When tossed to the side, most animals (5 out of 6) took the initial position in 1–2 sec. Exophthalmos was observed in 1 rat out of 6. The corneal reflex was normally expressed; the hind limbs were abducted in 5 out of 6 rats. The mean pain severity due to the tail pinching was 2.54±0.12 points, which did not differ from this index in the control group and was by 2.3 times higher than in Kindling rats without the activation of dopaminergic receptors of the striatum.

The structure of postural behavioral syndrome in rats with haloperidol intrastriatal microinjection was comparable to that of the intact rats of the control group.

We observed similar manifestations of postural behavior due to intrastriatal injection of muscimol. Under such experimental conditions, the rats mostly manifested components of free behavior specific for intact ones.

In the case of premature intrastriatal administration of bicuculin, the forelimbs of 5 of 6 rats when they were placed in the center of the horizontal platform were spread. When turned to the side, all rats took the original position in 1–2 s. Exophthalmos was observed in 1 rat out of 6. The corneal reflex was normally expressed, the hind limbs were abducted in 5 out of 6 rats. The mean pain severity due to the tail pinching was 2.66±0.12 points, which was comparable to this index in the control group and was by 2.3 times higher than in Kindling rats without the blockade of GABA-ergic receptors of the striatum.

Besides, it should be noted that the postural behavior of kindling rats (group 2) was identical in rats after the ketamine and atropine administration, and changed significantly after the naloxone administration, indicating the involvement of opioid receptors in its implementation at the stage of PCT-induced kindling.

2. Postural behavior of rats after the 24th convulsant injection.

At the time of reproduction of the Kindling model of epilepsy, the abduction of the fore and hind limbs in all animals is observed, i.e. the prevalence of the extensor position of the torso. Rats showed a normal inversion reflex and a corneal reflex. The tail tone was reduced in 7 rats out of 9. 2 rats out of 9 were able to maintain the bridge position, and 4 rats out of 9 managed to hold on to the vertical rod. The average pain severity due to the tail pinching was 3.84±0.21 points, which was by 1.5 times more than in the control observations ($p<0.05$).

In rats with intra-striated carbachol administration, the postural behavior of rats was characterized by the fact that when they were placed in the center of the horizontal platform, the forelimbs were spread (in 5 rats out of 6). When thrown to the side, all animals quickly took the original position. Exophthalmos was registered in all rats (6 out of 6). The corneal reflex was pronounced in most animals (5 out of 6). The hind limbs were abducted in 5 out of 6 rats. 50 % of the animals were able to maintain the bridge position

and hold on to the vertical rod. The mean severity of pain due to the tail pinching was 3.78±0.18 points, which was comparable to that of Kindling rats without the activation of cholinergic receptors of the striatum.

In rats with intrastriatal scopolamine administration, the severity of the postural-tonic syndrome was comparable to similar manifestations in Kindling rats.

In rats with intrastriatal injections of apomorphine and haloperidol, the features of postural behavior were equally pronounced with those recorded in the case of, respectively, the activation and blockade of the activity of striatal cholinergic receptors.

In rats that were given the intrastriatal muscimol injection, the postural behavior was characterized by the extensor positions of the fore and hind limbs of the torso when the rats were placed in the center of the horizontal plane. The rats manifested a violation of the inversion reflex and corneal reflex. Exophthalmos was registered in 1 rat out of 6, the tail tone was reduced. The rats were not able to maintain the bridge position and hold on to the rotating rod. The average pain severity due to the tail pinching was 2.16±0.18 points, which was similar to the corresponding control index and significantly different from the one in kindling rats ($p<0.05$).

In response to intrastriatal, microinjection of bicukulin all rats of the group manifested the prevalence of extensor position of the torso in the form of the abduction of the fore and hind limbs. All the rats had normal inversion and corneal reflexes. The tone of the tail was reduced. The bridge position was held properly by 2 rats out of 6, and 4 rats out of 6 managed to hold on to the vertical rod. The average severity of pain due to the tail pinching was 3.69±0.19 points, which was 43 % more than in the control observations, and did not differ from this index in Kindling rats ($p<0.05$).

It is important that the postural behavior of kindling rats (group 2) was identical to the one in rats after the administration of naloxone and ketamine, and changed significantly after the atropine administration, indicating the involvement of cholinergic receptors in its implementation at the stage of the completed PCT kindling.

3. Postural behavior of rats by the end of the kindling seizure-free period in the absence of convulsant injections.

At the end of the post-kindling period in rats of group 2, the prevalence of the extensor position of the torso in the form of the abduction of the fore and hind limbs is observed. The inversion reflex was impaired and there was no corneal reflex. Exophthalmos was registered. The tail tone was increased in all rats. The bridge position was held properly by 8 rats out of 9, and 2 rats out of 9 managed to hold on to the vertical rod. The mean severity of pain due to the tail pinching was 1.26±0.09 points, which was by 2.3 times more than in the control observations ($p<0.05$). Explosive reactions developed in 4 out of 9 rats.

Manifestations of the postural-tonic syndrome in the specified interval of the formation of kindling-induced convulsive activity in rats with intrastriatal microinjections of carbachol and scopolamine, apomorphine and haloperidol, as well as muscimol were similar to the ones in kindling rats without intrastriatal microinjections.

In response to intrastriatal microinjection of bicuculin in all rats of the group, the predominance of the flexor position of the torso in the form of erection of the fore and hind limbs is registered. In all rats, the inversion reflex was impaired and there was no corneal reflex. The tail tone was increased in 5 rats out of 6. The bridge position was held properly by 5 rats out of 6, and 3 rats out of 6 managed to hold on to the vertical rod. The mean severity of pain due to the tail pinching was 1.32±0.13 points, which was by 2.2 times less than in the control observations, and did not differ from this figure in Kindling rats ($p<0.05$).

It is worth mentioning that the postural behavior of rats in the postkindling stage without intrastriatal administration of drugs was identical in rats after the administration of ketamine and atropine, and changed significantly after the naloxone administration, indicating the involvement of opioid receptors in its implementation at the stage of formation of PCT-induced kindling.

Thus, our results indicate that in the dynamics of PCT-induced kindling in rats there are dramatic changes in postural behavior, which occur mainly due to the prevalence of opioid and neuroleptic mechanisms in the structure of this behavioral syndrome. Thus, in the phase of developed kindling, on the 18th day of the convulsant administration, opioid mechanisms dominated in the structure of postural behavior. At the time of the formed kindling, the structure of the postural-tonic behavioral syndrome was determined by neuroleptic mechanisms. In addition, at the end of the non-convulsive period of kindling, which is considered the period of the highest convulsive readiness, opioid mechanisms prevailed in the structure of the postural behavior of rats.

The neurotransmitter mechanisms of determining the manifestations of identified postural behavior were confirmed in experiments on its registration in the case of administration of naloxone, atropine and ketamine to rats – the pharmacological compounds whose mode of action is realized by the blockade of opioid and cholinergic systems and excitatory amino acids. Indeed, the hyperactivation of the opioid system at the time of kindling formation and by the end of the seizure period after its completion was blocked by the naloxone administration, which was confirmed by the change in the nature of postural-tonic behavioral syndrome from opioid to neuroleptic.

Analyzing the obtained data, we note that the effects of the modulation of the functional state of the striatum during three time intervals of chronic PCT-induced convulsive syndrome were investigated. Adding to this the complexity of analyzing the data obtained in the case of activation, on the one hand, and inhibition, on the other hand, of the activity of choline-, dopamine- and GABA-ergic neurotransmitter systems of the striatum, we would like to point out only the most interesting, in our opinion, pieces of data that require attention.

First, at the time of kindling formation, i.e., on the 18th day of convulsant administration, there is an increase in GABA-ergic and inhibition of dopaminergic neurotransmission activity of the striatum together with the inhibition of its cholinergic mediation. These data indicate the proconvulsive activity of the striatum in the dynamics of the picrotoxin kindling formation. Another point that deserves attention is the involvement of the above neurotransmitter systems in the implementation of the disorders of postural behavior induced by chronic convulsive activity. Lastly, in our opinion, it is worth mentioning that the normalization of postural behavior in the case of intrastriatal microinjections of apomorphine, which activates dopaminergic receptors, and bicuculin, which blocks the activity of GABA-ergic mediation. The aforementioned data speak in favor of dopamine and GABAergic neurotransmitter mechanisms, which directly determine the excitability of the brain of animals and the nature of non-convulsive disorders at the time of chronic convulsive syndrome formation.

Secondly, at the time of the formed kindling neuroleptic components dominate in the structure of behavioral manifestations of animals. At this time, there is a functional enhancement of cholinergic and dopaminergic neurotransmission of the striatum together with the suppression of its GABA-ergic mechanisms. Importantly, the structure of postural-tonic behavioral syndrome is normalized under such conditions after the inhibition of choline and dopaminergic activity of striatum neurons by, respectively, scopolamine and haloperidol, as well as after activation of GABA-ergic striatal neurons by muscimol.

Moreover, the third one: by the end of the non-convulsive period, during which, as is known, the activity of the pathological epileptic system becomes most pronounced, the hyperactivation of opioid mechanisms is noted in the structure of postural behavior. At this time in the studied rats, the activation of choline and dopaminergic striatum mediation and inhibition of its GABA-ergic activity is observed. However, these changes in postural behavior were eliminated only after the intrastriatal bicukulin administration.

It is quite remarkable that our data are fully consistent with the concept of the striatal proconvulsive importance and its involvement in the formation of the pathological epileptic system during the pharmacological kindling formation [3].

The cortico-striatal mechanisms were shown to be involved into the excitability processes regulation throughout chronic convulsive activity of different forms modeling [2]. One should mentioned both opioid and neuroleptic mechanisms hyperexcitability undulating dynamics in chronic epileptogenesis induced by pharmacons which mechanisms of convulsive activity realization realizes through GABA-, cholin-ergic mediation, as well as the system of excitatory amino acids comprometation [2, 3]. Our data also correspond to the results showed antiepileptic system activity wave-like pattern during epileptogenesis and immediately by the end of convulsants administration [8, 10].

It is important that similar behavioral disorders were noted in the dynamics of both pentylenetetrazole and pilocarpine kindling [9], which indicate pathophysiological mechanisms of behavioral disorders similarity in chronic convulsive syndrome dynamics. Therefore, we are forced to admit that the therapy of epilepsy today is more symptomatic and there is no reliable strategy for its prevention [1].

Hence, we consider it important to study the severity, time dependence, quantitative and qualitative characteristics of nonconvulsive, interictal behavioral disorders in the dynamics of the formation of chronic convulsive syndrome, since the diagnosis of behavioral disorders is an easy and effective methodological technique that will make it possible to diagnose with confidence subclinical processes of excitability disorders in the brain [1, 4, 6].

The prospects for further development, in our opinion, are to study other types of behavior – motor, emotional, swimming, cognitive – and their disorders during the specified time intervals of the formation of chronic epileptic activity for the use of certain behavioral disorders as an early diagnosis of epilepsy, when motor convulsive manifestations are absent, and probable behavioral disorders do not reach their maximum intensity.

Conclusions

1. Opioid mechanisms prevail in the structure of postural behavioral reactions of animals during the formation (on the 18th day) of PCT-induced chronic convulsive syndrome. The strengthening of GABA-ergic and inhibition of the activity of dopaminergic neurotransmission of the striatum together with the inhibition of its cholinergic mediation determine the manifestations of the postural-tonic behavioral syndrome at this time.

2. In the formed picrotoxin-kindling model (on the 24th day), the neuroleptic components predominate in the structure of postural behavioral reactions. The manifestations of postural-tonic behavioral syndrome at this time are marked by increased cholinergic and dopaminergic neuromediation of the striatum together with the suppression of its GABA-ergic mechanisms.

3. At the end of the seizure-free period, after a 14-day interval after the end of kindling, opioid mechanisms prevail in the structure of late-tonic behavioral responses of animals. At this time, the studied rats manifest the activation of choline and dopaminergic striatum mediation and the inhibition of its GABA-ergic activity.

4. The obtained data indicate the hyperactivation of the striatum under the conditions of the development of PCT-induced chronic convulsive activity, the functional activity of which depends on the term of the convulsive syndrome manifestation.

5. The study of non-convulsive types of motor, emotional, swimming, cognitive behavior and their disorders during the specified time intervals of the formation of chronic epileptic activity is important for the use of certain behavioral disorders as an early diagnosis of epilepsy when the motor seizure disorders are absent and the probable behavior disorders do not reach maximum intensity.

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Стаття надійшла 29.03.2020 р.