DOI 10.26724/2079-8334-2021-1-75-176-181
UDC 616.61:591.3:546.48:612.6

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EFFECT OF METAL CITRATES ON INDICATORS OF THE EMBRYOTOXICITY OF CADMIUM SALTS IN RATS WITH COMBINED INTRODUCTION

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The aim of the study was to determine the effect of metal citrates (cerium, zinc, iron) when combined with cadmium salts (chloride/citrate) on the embryotoxicity of cadmium in rats. The aim of the study was to determine the effect of metal citrates (cerium, zinc, iron) when combined with cadmium salts (chloride/citrate) on the embryotoxicity of cadmium in rats. Embryotoxic effects of test substances in groups were calculated and compared according to the following indicators: number of embryos, total, preimplantation, postimplantation embryonic mortality. Comparison of the embryotropic properties of cadmium chloride and cadmium citrate in the groups of isolated administration revealed a higher level of embryotoxicity of cadmium chloride. In the groups of combined administration, the greatest reduction in embryotoxicity was determined in the groups of the combination of cadmium with iron citrate for all studied indicators.

Key words: embryogenesis, cadmium, cerium citrate, iron citrate, zinc citrate, embryonic mortality.

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ВПЛИВ ЦИТРАТІВ МЕТАЛІВ НА ПОКАЗНИКИ ЕМБРІОТОКСИЧНОСТІ СОЛЕЙ КАДМІЮ У ЩУРІВ ПРИ КОМБІНОВАНОМУ ВВЕДЕННІ

Метою дослідження було визначення впливу цитратів металів (церію, цинку, заліза) при комбінованому введенні з солями кадмію (хлориду/цитрату) на показники ембріотоксичності кадмію у щурів. Окрім контрольної групи, були 2 групи ізольованого введення кадмію і 6 груп комбінованого введення солей кадмію з цитратами металів (церій, цинк, залізо). Ембріотоксичну дію досліджуваних речовин в групах розраховували і порівнювали за наступними показниками: кількість ембріонів, загальна, доімплантаційна, післяімплантаційна ембріональна смертність. Порівняння ембріотропних властивостей хлориду кадмію та цитрату кадмію в групах ізольованого введення виявило більш високий рівень ембріотоксичності хлориду кадмію. У групах комбінованого введення найбільше зниження показників ембріотоксичності визначалося в групах комбінації кадмію з цитратом заліза по всіх досліджуваних показниках.

Ключові слова: ембріогенез, кадмій, цитрат церію, цитрат заліза, цитрат цинку, ембріональна смертність.

The work is a fragment of the research project "Morphofunctional peculiarities of organs and tissues under the influence of external and internal factors", state registration No. 0120U105219.

The current level of development of industrial technologies does not allow to move to environmentally friendly production, and one of the most common environmental pollutants are heavy metal ions, including cadmium and its compounds [1, 2]. Significant anthropogenic contribution to environmental pollution leads to the crossing of the upper limit of the maximum allowable quantitative concentrations of cadmium in a number of industrial areas both in our country and outside Ukraine in soils, water, air and food [4]. The maximum allowable concentration of cadmium in the atmosphere is 0.3 μg/m, in water of water sources 0.001 mg/l, in sandy and sandy soils acidic and neutral 0.5, 1.0 and 2.0 mg/kg, respectively. The World Health Organization (WHO) has set a permissible amount of cadmium in the body of 6.7-8 μg/kg [5, 6, 10].

Based on the data obtained in experiments on laboratory animals, it is shown that in the public consciousness the danger of cadmium is unjustifiably underestimated, the insufficiency and limited justification of the embryotoxicity of heavy metals, in particular cadmium, encourages researchers to actively study the effect of different doses of this ecotoxicant and different ways of getting metal into the body on the indicators of embryogenesis and the functioning of the reproductive system [3, 7, 9]. It is important to search for new trace elements that may have pronounced bioanthogonistic properties in relation to the embryotoxicity of cadmium compounds [8, 9].

The purpose of the study was to determine the effect of metal citrates (cerium, zinc, iron) when combined with cadmium salts (chloride / citrate) on the embryotoxicity of cadmium in rats.

Materials and methods. Low doses of cadmium salts were selected for experimental studies, which can be compared with the corresponding real content in the daily diet of women in the industrial

region. In the experiment, female rats with a certain gestational age were divided into groups as follows: 1 – control (number of females – n=16, of which 8 were withdrawn from the experiment on the 13th day of pregnancy, and 8 on the 20th; number of embryos – n_{13}=76; n_{20}=77); 2 – isolated administration of cadmium chloride at a dose of 1.0 mg/kg body weight of females (number of females – n=16; number of embryos – n_{13}=65; n_{20}=62); 3 – isolated administration of cadmium citrate at a dose of 1.0 mg/kg body weight of females (number of females – n=16; number of embryos – n_{13}=69; n_{20}=70); 4 – combined administration of cadmium chloride at a dose of 1.0 mg/kg + cerium citrate at a dose of 1.3 mg/kg (number of females – n=16; number of embryos – n_{13}=73; n_{20}=73); 5 – combined administration of cadmium citrate at a dosage of 1.0 mg/kg + cerium citrate at a dose of 1.3 mg/kg (number of female rats – n=16; number of embryos – n_{13}=71; n_{20}=71); 6 – combined administration of cadmium chloride at a dose of 1.0 mg/kg and zinc citrate at a dose of 1.5 mg/kg (number of female rats – n=16; number of embryos – n_{13}=74; n_{20}=74); 7 – combined administration of cadmium citrate at a dose of 1.0 mg/kg and zinc citrate at a dose of 1.5 mg/kg (number of female rats – n=16; number of embryos – n_{13}=68; n_{20}=69); 8 – combined administration of cadmium chloride at a dose of 1.0 mg/kg and iron citrate at a dose of 1.5 mg/kg (number of females – n=16; number of embryos – n_{13}=74; n_{20}=75); 9 – combined administration of cadmium citrate at a dose of 1.0 mg/kg and iron citrate at a dose of 1.5 mg/kg (number of females – n=16; number of embryos – n_{13}=75; n_{20}=73).

Thus, in addition to the control group, there were 2 groups of isolated cadmium administration and 6 groups of combined administration of cadmium salts with metal citrates (cerium, zinc, iron). The cadmium chloride solution had an ionic form. In our experimental models we used solutions of cadmium, iron, cerium and zinc citrates obtained by aquananotechnological methods.

According to the generally accepted instructions for conducting experimental work on chronic exposure to xenobiotics, solutions of the test substances were administered to pregnant female rats orally through a tube once a day from the 1st to the 19th day of pregnancy [7]. During the experiment, the dynamics of the condition, behavior of female rats and changes in body weight were recorded, and on the 13th and 20th day of pregnancy the animals were sacrificed using thiopental anesthesia. Rats were removed from the uterus, checked for the test "living-dead", weighed, counted the number of corpora lutea in the ovaries of females and their correspondence to the number of embryos in each corner of the bicornuate uterus.

The embryotoxic effect of isolated and combined effects of test substances in groups was calculated and compared according to the relevant indices:

1. Total embryonic mortality=

where A – number of live embryos, B – the number of corpora lutea of pregnancy.

2. Preimplantation mortality=

where A – number of live embryos, C – number of dead (resorbed) embryos, B – the number of corpora lutea of pregnancy.

3. Postimplantation mortality=$\mathrm{PIM} = \frac{C}{A+C}$

where A – number of live embryos, C – number of dead resorbed) embryos.

4. Number of embryos per 1 female (M±m)

The research was performed in accordance with the principles of the International Code of Medical Ethics (1983), "General ethical principles of animal experiments" (Kyiv, 2001) in accordance with the provisions of the "European Convention for the protection of vertebrate animals used in experiments and other educational purposes".

Processing of the obtained experimental data was carried out by the method of variation statistics using the program "Microsoft Exel". Significance of differences in the obtained morphometric parameters was determined using Student's t-test.

Results of the study and their discussion. Calculation of the obtained experimental data revealed the embryotoxicity of cadmium chloride and citrate when isolated, but the level of embryotoxicity of cadmium salts was different. Isolated administration of cadmium chloride led to a decrease in the average number of embryos and an increase in all types of embryonic mortality on both the 13th and 20th days of embryogenesis compared to the control. The number of embryos on the 13th day in the experimental group exposed to cadmium chloride was significantly lower ($p<0.05$) and was 8.12±0.31 against 9.50±0.20 of the control group. In the groups of combined exposure, this indicator showed a modifying effect of metal citrates on the embryotoxicity of cadmium chloride, that is the number of embryos was restored (fig. 1). The highest level of compensatory effect on the embryotoxicity of cadmium chloride according to this indicator was determined in the group of combined exposure to iron citrate, which had no significant difference with the control.

On the 20th day of embryogenesis, the mean value (M±m) of the number of embryos tended to decrease in the group of isolated exposure and was restored in the groups of combined administration of

the studied substances. Namely: in the group of isolated exposure to cadmium chloride, the number of embryos continued to decrease, which is logical due to the prolongation of the negative factor and was 7.75±0.40 against 9.50±0.20 in the control. This difference was significant, $p<0.001$. In the groups of combined exposure, the number of embryos was significantly higher compared to the group of isolated administration of cadmium chloride, but did not have a significant difference with the control, which we also regard as a modifying effect of biometal citrates on the toxicity of cadmium chloride in the experiment with intragastric administration in these doses (Fig. 1).

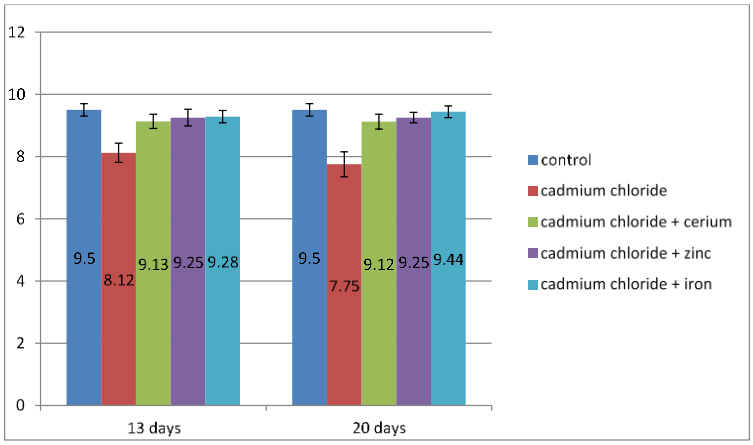

Fig.1. Indicators of the average values of the number of live embryos of rats in the control and experimental groups with the introduction of cadmium chloride on the 13th and 20th day of pregnancy.

The analysis of the calculations of total embryonic mortality in the groups of isolated and combined administration of cadmium chloride revealed the following trend. At both terms of the study, the highest rate of TEM was also determined in the group of isolated administration of cadmium chloride: on the 13th day it was equal to 0.22±0.02 against the control 0.05±0.02, and on the twentieth day increased in 5 times to 0.25±0.02 (in the control – 0.05±0.02).

The increase in the studied indicator is the result of continued daily administration of cadmium chloride to pregnant females, which provoked increased cadmium intoxication and as a protective mechanism - self-abortion by the female embryos (resorption of embryos). In the groups of combined administration of cadmium chloride with metal citrates, the rate of total embryonic mortality at both observation periods decreased more than twice in comparison with the isolated introduction, which indicates the compensatory effect of cerium, zinc and iron citrates on the embryotoxicity of cadmium chloride in an experiment on rats (fig. 2).

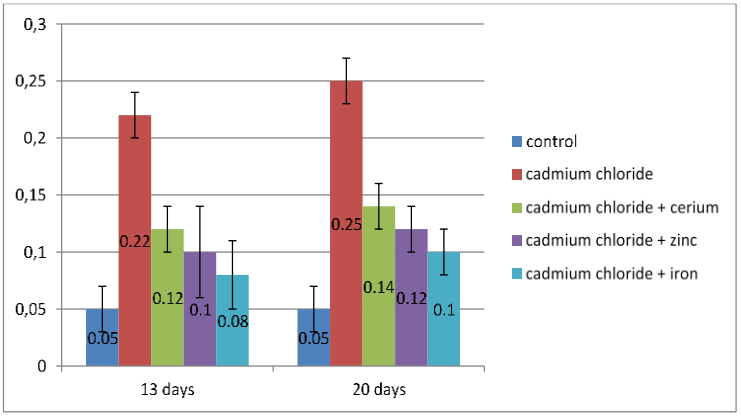

Fig. 2. Experimental data of total embryonic mortality on the 13th and 20th days of embryonic development of rats in control and experimental groups with the introduction of cadmium chloride.

The obtained results showed that the greatest decrease in occurred in the group of combined administration of cadmium chloride with iron citrate at both periods of embryogenesis studied by us. This figure in this group on the 13th day significantly exceeded the control and was 0.08±0.03, and on the 20th day twice exceeded the control values of 0.10±0.02 ($p<0.05$). The administration of zinc citrate on the background of cadmium intoxication also reduced overall embryonic mortality in the group, but to a lesser extent than the introduction of iron citrate (Fig. 2). Cerium citrate in combination with cadmium on days 13 and 20 reduced overall embryonic mortality by 1.8-fold compared with isolated administration of cadmium chloride. Thus, the degree of reduction of embryotoxicity of cadmium chloride in the groups of combined administration is quite pronounced, but the level of compensatory effect of individual citrates on the TEM is different.

The formation of total embryonic mortality is influenced by indicators of preimplantation and postimplantation mortality. Embryo implantation in rats occurs on 4-5th day of embryogenesis and the influence of negative factors of both endogenous and exogenous origin can disrupt this process. In our experiment, the highest level of PrIM was determined in the group of isolated administration of cadmium chloride and was 0.13±0.03 on the 13th day , while in the control group this indicator was equal to 0.04±0.02, ie the difference was significant $p<0.05$. On the 20th day, the isolated effect of cadmium chloride formed the PrIM index at the level of 0.14±0.03 (control – 0.02±0.02) ($p<0.001$), which is logical under conditions of continued exposure to the negative factor, and the lowest value of this indicator among

the groups of combined administration was determined in the group of exposure to cadmium chloride with iron citrate (0.04±0.02) and cadmium chloride with zinc citrate – 0.05±0.02.

Postimplantation mortality rates in the cadmium chloride experimental groups were distributed as follows: the highest level of PIM was determined in the group of isolated administration of cadmium chloride – 0.09±0.01 (control – 0.01±0.01) 13th day, 0.12±0.02 (control – 0.02±0.02) 20th day. In the groups of combined administration, a decrease in the number of resorptions in the rat uterine horns (PIM) was determined in comparison with the isolated effect of cadmium on both studied terms of embryogenesis (table 1).

Table 1

Mean values of post-implantation embryonic mortality in control and experimental groups with exposure to cadmium chloride on the 13th and 20th day of rat embryogenesis

Control		Cadmium chloride		Cadmium chloride+cerium citrate		Cadmium chloride+zinc citrate		Cadmium chloride+iron citrate	
day 13	day 20	day 13	day 20	day 13	day 20	day 13	day 20	day 13	day 20
0.01±0.01	0.02±0.02	0.09±0.01	0.12±0.02	0.07±0.02	0.08±0.02	0.04±0.02	0.07±0.02	0.05±0.02	0.06±0.02

Notes: * the significance of the difference with the control – $p<0.05$; # the significance of the difference with the group of isolated administration of cadmium chloride – $p<0.05$;

Thus, the analysis of the basic indicators of embryogenesis in groups with the introduction of cadmium chloride demonstrated the compensatory effect of cerium, zinc and iron citrates on the embryotoxic properties of cadmium chloride when combined with metal citrates at these doses in an experiment in rats.

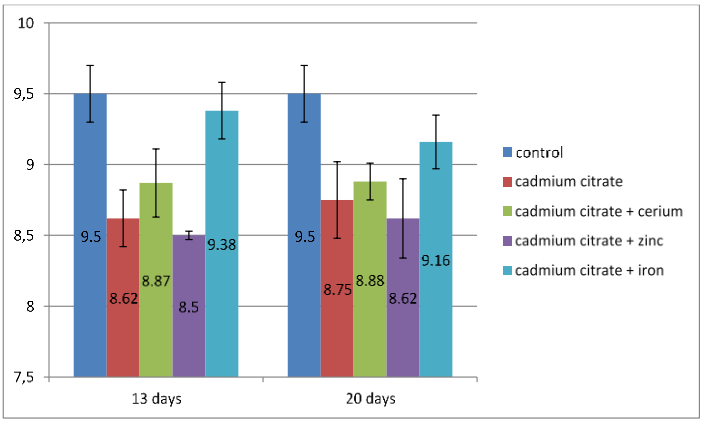

Fig.3. The average number of live rat embryos on the 13th and 20th days of embryonic development in the control and experimental groups on the effects of cadmium citrate.

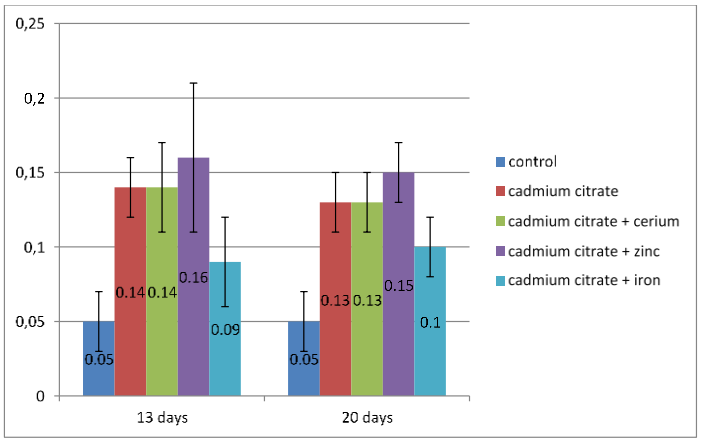

Fig. 4. The average rates of total embryonic mortality on the 13th and 20th days of embryonic development of rats in the control and experimental groups with the introduction of cadmium citrate.

The following results were determined in the cadmium citrate groups. The isolated administration to female rats of cadmium citrate had higher mean embryo counts than the cadmium chloride group, indicating a less toxic effect of cadmium citrate on the overall course of embryogenesis despite the identity of the dose of cadmium. On the 13th day, the number of embryos was equal 8.62±0.20, and on 20th day – 8.75±0.27. In the groups of combined administration, there was an increase in the number of embryos in both terms studied, which we regarded as a decrease in embryotoxicity of cadmium citrate with cerium, zinc, iron citrates. According to this criterion, the highest compensatory effect was observed in the group of combined administration of cadmium citrate and iron citrate, in which on the 13th and 20th day the number of embryos did not have a significant difference with the control values (fig. 3).

Examining the rates of total embryonic mortality and comparing them in the groups with isolated and combined administration of cadmium citrate, it was determined that the highest rate of TEM was observed in the group of combined administration of cadmium with zinc.

Such results have come as a surprise because zinc and its compounds are essential and widely used in medical practice. In this group on the 13th day the TEM was 0.16±0.05, and on the 20th day 0.15±0.02, which was not significantly higher than in the group of isolated administration of cadmium citrate. In the groups of combined administration of cadmium citrate with cerium/iron citrates, the indicators of TEM were lower (iron citrate) or equal to (cerium citrate) indicators of the group of isolated administration of cadmium citrate (fig. 4).

Indices of preimplantation and postimplantation embryonic mortality in the groups of cadmium citrate administration had the following trend (table 2).

Table 2

Mean rates of preimplantation (PrIM) and postimplantation (PIM) embryonic mortality in control and experimental groups with exposure to cadmium citrate on the 13th and 20th days of rat embryogenesis

Groups	Control		Cadmium citrate		Cadmium citrate+cerium		Cadmium citrate+zinc		Cadmium citrate+iron	
Day	**13**	**20**	**13**	**20**	**13**	**20**	**13**	**20**	**13**	**20**
PrIM	0.04± 0.02	0.02± 0.02	0.08± 0.02*	0.06± 0.02	0.07± 0.03	0.013± 0.01*	0.11± 0.05*	0.07± 0.02*	0.04± 0.02	0.045± 0.02
PIM	0.01± 0.01	0.02± 0.02	0.06± 0.02	0.08± 0.03	0.08± 0.02	0.12± 0.02	0.07± 0.02	0.08± 0.02	0.05± 0.02	0.06± 0.02

Notes: * the significance of the difference with the control – $p<0.05$;

Thus, the analysis of the obtained results revealed that in the groups of combined administration with cadmium citrate the greatest modifying effect on the embryotoxicity of cadmium is exerted by iron citrate, namely, the indicator of its PrIM has no significant difference with the control on both studied terms, and the PIM is higher than the control, but lower than the indicators of the group of isolated administration of cadmium citrate.

Thus, the analysis of the obtained experimental results revealed that the effects of cadmium chloride (ionic solution) and cadmium citrate (nanoaquachelate form) in the same doses of cadmium have different degrees of embryotoxicity with intragastric daily administration. Cadmium chloride has a higher level of embryotoxicity, which causes higher levels of preimplantation, postimplantation and total embryonic mortality and reduces the number of embryos in the litter. The obtained data of the introduction of cadmium salts in the test dose, or close to it and the method of administration correlate with the data obtained by other researchers [2, 3]. The search for new possible bioanthogonists of cadmium salts in humans or animals among micronutrient citrates is currently a very important issue, which is gaining increasing interest among experimenters [7]. The results of reducing the embryotoxicity of cadmium when combined with citrates of biometals provide prospects for the identification of new cadmium bioanthogonists. However, in the data presented in the scientific literature, there are no results of daily administration of the studied factors throughout the pregnancy of rats. Most researchers determine that additional studies, especially those involving environmentally significant doses, are needed to confirm the toxic and epigenomic effects of prenatal cadmium on health in childhood and later. [10]. Unfortunately, we have not identified work on the combined effect of iron, cerium and zinc citrates with cadmium salts on the studied indicators of embryogenesis. Such experiments were conducted for the first time.

Conclusion

Comparison of the embryotropic properties of cadmium chloride and cadmium citrate in the groups of isolated administration revealed a higher level of embryotoxicity of cadmium chloride according to classical criteria in an experiment on rats. The highest level of total, preimplantation and postimplantation embryonic mortality were determined in the cadmium chloride exposure group.

In the groups of combined administration of citrates of the studied metals with cadmium, a significant decrease in embryotoxicity was determined in the groups of the combination of cadmium with iron citrate for all studied indicators. Iron citrate in this dose can be considered as a new bioanthogonist of embryotoxic properties of cadmium salts.

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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