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CORRECTION OF THE WAKE-SLEEP CYCLE BY INTRANASAL ADMINISTRATION OF DOPAMINE IN MODELING OF THE PRECLINICAL STAGE OF PARKINSON'S DISEASE IN RATS

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Abstract

Sleep disorders, which are among the earliest and most sensitive non-motor manifestations of Parkinson's disease (PD), are not diagnosed in 40–50 % of patients and are not subject to the necessary correction. In this regard, the ineffectiveness of a late start of treatment, when more than 50 % of dopamine-producing neurons are already affected, dictates the need to search for and develop approaches to the prevention and slowdown of neurodegenerative pathology at the preclinical stages of its development using adequate experimental models. Taking into account the low bioavailability of dopamine (DA) and data on the advantages of the intranasal route of administration in comparison with oral and parenteral methods of drug delivery to the CNS, the aim of the work was to study the neurophysiological features of the wake-sleep cycle as early manifestations of nigrostriatal insufficiency and the effect of intranasal administration of DA on the quality of sleep during the formation of the preclinical stage of PD in rats. It was shown that under the conditions of modeling PD, the cyclic organization of sleep with a predominance of incomplete cycles against the background of hyperproduction of slow-wave sleep and REM phases are early manifestations of nigrostriatal insufficiency. Course administration of DA at a dose of 3 mg/kg is accompanied by the normalization of sleep quality in the form of reduction (by 76 %) in the number of incomplete cycles. The preventive orientation of the obtained effects may indicate a certain therapeutic potential of intranasal delivery of DA to the brain, aimed at slowing down the processes of neurodegeneration and possibly delaying its clinical manifestation.

Keywords: model of Parkinson's disease, wake-sleep cycle, intranasal administration of dopamine.

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1. Introduction

Parkinson's disease (PD) is a steadily progressive disease with the gradual development of neurodegenerative processes characterized by the presence of α-synuclein aggregates with Lewy bodies in various areas of the brain, which is associated with dysfunction of neurotransmitter systems. These processes precede the death of dopaminergic neurons in cpSN, that is the main pathophysiological sign of PD and underlies progressive neurodegeneration, which causes its diverse symptoms in the form of non-motor and motor disorders [1, 2] in order. Initially, synucleinopathies in the CNS appear in the anterior olfactory structures and the nucleus dorsalis n. vagi, in the descending raphe system and the blue spot (*locus coeruleus*), and then in the cpSN. It is known that the *locus coeruleus*, which has extensive innervation throughout the brain, is a fundamental neuromodulator, participating in reactions to stress, providing emotional memory and controlling motor, sensory, and vegetative functions [3, 4].

Due to the fact that motor disorders appear as a result of a significant decrease in dopamine (DA) in the striatum, when more than 50 % of dopamine-producing neurons are already affected, the pathogenesis of PD includes a prodromal period characterized by non-motor symptoms in the form of impaired sense of smell, dysregulation sensory, vegetative, emotional, motivational, cognitive functions and sleep disorders, which are considered as markers of its early diagnosis [5–8].

Sleep disorders, the frequency of which in patients with PD reaches 40–98 %, are among its most significant non-motor manifestations [9–11], including those at the preclinical stage of neurodegenerative pathology development [12]. Moreover, parasomnia in the form of behavioral disorders in the phase of paradoxical sleep (REM) is considered the most sensitive and specific predictor of PD, far ahead of motor manifestations [13]. There are data on the variability of changes in the stages of slow-wave sleep (NREM) and the duration of the phase of paradoxical sleep (REM) [14]. It has been shown that changes in the wake-sleep cycle in PD are caused, in particular, by an imbalance of neurotransmitters in the monoaminergic and cholinergic systems of the brain due to degeneration of the brainstem nuclei and structural and functional disorders in the system of descending connections of hypothalamic neurons with dopaminergic neurons of the ventral tegmentum, as well as ascending stem-thalamo-cortical projections [15, 16], which may indicate the endogenous nature of the causes of sleep disorders. Its unsatisfactory quality is one of the leading factors that worsen the quality of life of patients with early and advanced stages of PD, which in 40−50 % of cases are not diagnosed and not subjected to appropriate correction [17–22]. This is related to the ineffectiveness of the late start of treatment of the disease, which dictates the need to search for and develop new approaches to the prevention and slowdown of neurodegenerative pathology at the preclinical stages of its development in the direction of studying the early symptoms of nigrostriatal insufficiency using adequate experimental models.

The main link in the pathogenesis of PD is impaired dopaminergic neurotransmission in the nigrostriatal system of the brain [23, 24] with a decrease in DA in the striatum, which leads to the development of motor symptoms: hypokinesia, bradykinesia, rigidity, and rest tremor [25]. Since exogenous DA is unable to cross the blood-brain barrier (BBB), monoamine oxidase B inhibitors, dopamine receptor agonists, and DA precursor L-DOPA are used for their treatment. However, the progression of the disease is accompanied by a decrease in sensitivity to them and the occurrence of side effects, which significantly limits the possibilities of therapy [26, 27].

With this in mind, studies of the effectiveness of intranasal drug delivery as an alternative to oral and parenteral routes of administration for dosing potent CNS-targeting drugs, as well as for their entry into the brain bypassing the main physiological barriers: the blood-brain (BBB) and liquor (B-CSF-B), which limit the passage of xenobiotics into the brain and their transport between CSF and the brain parenchyma [28–35].

Molecular diffusion through the trigeminal nerve and the olfactory pathway from the nasal cavity provides direct access to the brain and creates a favorable pharmacokinetic/pharmacodynamic profile of drugs acting on the CNS [36, 37]. The advantages of the intranasal route of drug administration are non-invasiveness, shorter time to effect and higher bioavailability, which provides a significant reduction in the effective oral dose to 0.01–1.00 %, which facilitates the achievement of the required concentration of pharmacological drugs in the brain parenchyma.

The aim of this work was to study the neurophysiological features of the structural and functional organization of the wake-sleep cycle as early manifestations of neurodegenerative pathology, as well as the effect of course intranasal administration of DA on the quality of sleep during the formation of the preclinical stage of PD in rats.

2. Materials and methods

The procedures with experimental animals were approved by the Commission on Ethics and Deontology of the SI «Institute of Neurology, Psychiatry and Narcology of National Academy of Medical Sciences of Ukraine» (INPN NAMS of Ukraine, Kharkiv, protocol No. 12 of 04.12.2020) and performed in accordance with the «General Ethical Principles of Animal Experiments» (Kyiv, Ukraine, 2011), «The procedure for conducting experiments on animals by scientific institutions» (No. 249 of 01.03.2012), and the Law of Ukraine «On protection of animals from cruel treatment» (No. 3447 IV of 21.02.2006).

Chronic experimental studies were carried out using 8 white male rats Wistar adult (10–12 months) of age, body weight 318.8±6.8 g, grown in the vivarium of the INPN NAMS of Ukraine (Kharkiv) and kept 4 individuals in plastic cages 40×75×25 cm in size at t=20–25 °C and air humidity of 60 % in conditions of natural daily lighting with free access to food and water. All exper-

imental animals were stochastically divided into two groups: group I – PD model+solvent (control, *n*=4); group II – PD model+DA (*n*=4).

All animals underwent stereotaxic implantation of long-term electrodes for bipolar recording of electroencephalograms (nichrome in glass insulation with a non-insulated tip diameter of 100 microns) in brain structures: the hippocampus (field CA-1), cpSN, in accordance with the atlas rat brain [38]. Coordinates of cpSN were corrected taking into account the data of G. Paxinos, Ch. Watson [39]. Cortical nichrome electrodes were placed epidurally in the frontal-parietal region, and an indifferent electrode was placed in the nasal sinus bone. Steel electrodes for recording myograms were stationary fixed in the oblique muscle of the neck. The operations were performed under sterile conditions under general anesthesia (sodium thiopental at a dose of 50 mg/kg of animal body weight).

Polygraphic recording of sleep was carried out during the period of moderate emotional activity of rats (from 10^{00} to 15^{00}) in natural light conditions [40]. Electroencephalograms and myograms in bipolar leads were recorded using the diagnostic complex «Neuron-Spectrum» with a block of electroencephalographic signals («Spectromed-Ukraine», Kharkiv). The averaged values of the structural and functional organization of somnograms lasting from 2.0 to 3.5 hours, obtained over 3 consecutive days, starting from the 5–6^{th} day after neurosurgical intervention with an interval of 5 days up to 30–35 days of the chronic experiment, were used as individual initial indicators (background).

The non-motor stage of PD was then simulated by partial bilateral electrolytic injury of cpSN using a current of 3 to 5 μA and a voltage of 12 V from 5 to 6 seconds. The anode was alternately connected to stationary electrodes located in the cpSN symmetrically in the two hemispheres of the brain. The cathode was placed in the oral cavity of the animal, on the tongue. The day of destruction was designated as day zero (0) of the chronic experiment.

Neurophysiological studies included electroencephalographic recording of 60 dreams in the dynamics of the formation of the PD model, starting from the fifth day after the partial injury of cpSN with an interval of 5 days up to 30–35 days of the chronic experiment.

A solution for intranasal administration of DA was prepared *extemporae* using crystalline DA hydrochloride («Sigma-Aldrich», Germany) and bidistilled water and kept on ice (–20 °C) protected from light. Starting from the first day after the injury of cpSN, all experimental animals in the state of the wake 2 times a day (at 9^{00} and 16^{00}) were intranasal administration with an aqueous solution of DA at a dose of 3 mg/kg [29, 41, 42] or a solvent in a volume of 20 μl into each nostril with an application depth of 2 mm. Before administration, the solution was heated to a comfort temperature (22 °C).

Statistical processing of the results to determine the significance of differences between the comparison groups was carried out using the «Excel» application (non-parametric Student's t-test).

3. Results

Visual ethological observations showed that on the first day after the destruction, against the background of a satisfactory somatic condition of the animals, moderately pronounced motor disorders were noted in the form of a decrease in general motor activity (71.4 %), inclination of the trunk or neck, changes in gait (28.6 %), and some rigidity of the muscles of the hind limbs and torso (57.1 %), increased tone of the tail (57.1 %), a tendency to arena "running" (28.6 %) and imposed stereotypical head movements (71.6 %) (**Fig. 1**).

Such behavioral deviations were obviously associated with traumatic intervention and injury to the brain tissue in the modeling of nigrostriatal insufficiency and were caused both by the direct death of dopaminergic neurons and by perifocal edema due to neuroinflammation in the zone of partial electrolytic injury of cpSN contributing to the induction of neurodegenerative processes. However, the dynamics of their manifestations with a significant reduction already by day 5 and further regression, up to complete disappearance by day 10–15, indicate the transient nature of motor disorders, confirming the adequacy of the used model of the initial non-motor stage of PD.

Structural and functional organization of the wake-sleep cycle under the conditions of PD modeling (group I, control) (**Fig. 2, *a***) was characterized by no changes up to 5 days after the injury

of cpSN, subsequently demonstrating a redistribution of indicators of the phases and stages of slow-wave sleep, which stabilized in 10 days certain quantitative ratios.

This was accompanied by a significant ($p \leq 0.01$) reduction in the time of wake (by 61 %) and an increase in the representation of paradoxical (REM) sleep (by 160 %) from the 10th day of the formation of the non-motor stage of PD, stabilizing over the further observation period, along with a trend towards an increase in the production of deep slow sleep (NREM3) (**Fig. 3, *a***).

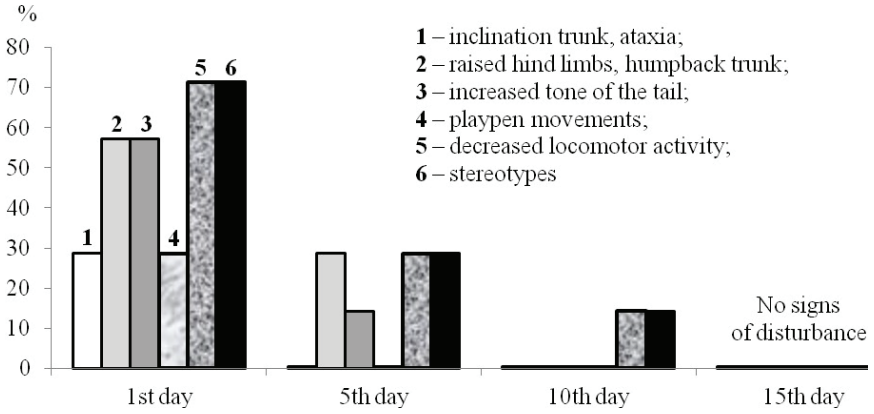

Fig. 1. Dynamics of representation of motor changes in the process of formation of the non-motor stage of PD by bilateral electrolytic injury of the cpSN:
X-axis – observation period; *Y*-axis – relative representation of signs

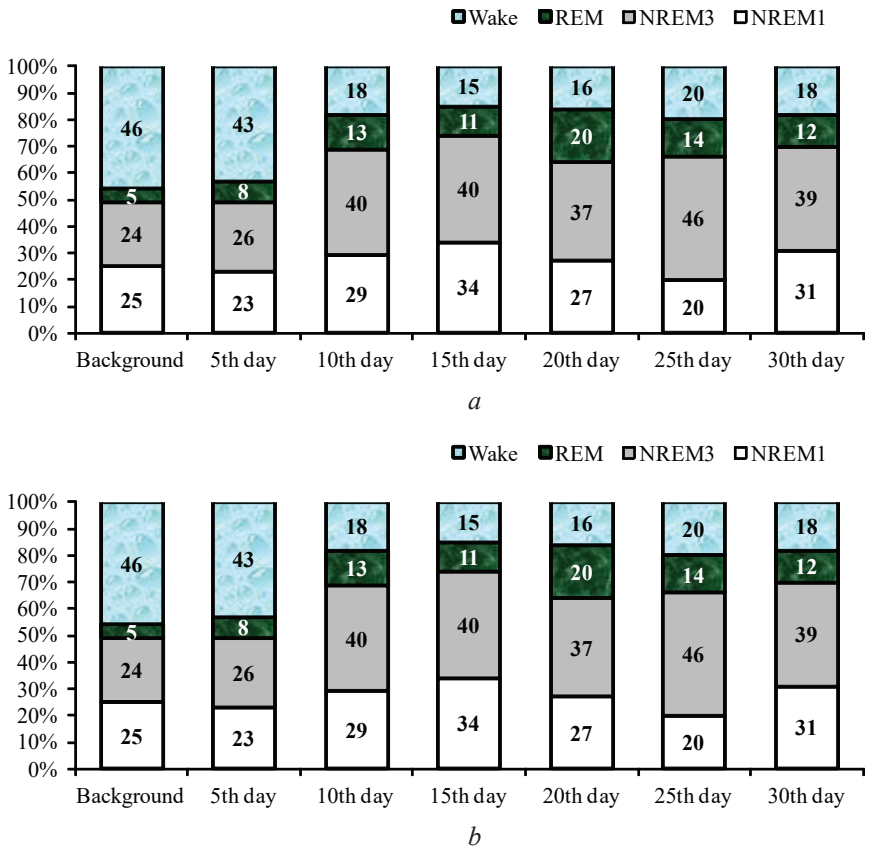

Fig. 2. Structural and functional organization of the wake-sleep cycle in the dynamics of the formation of the non-motor stage of PD: *a* – model of Parkinson's disease (control);
b – model of Parkinson's disease+intranasal administration of DA solution

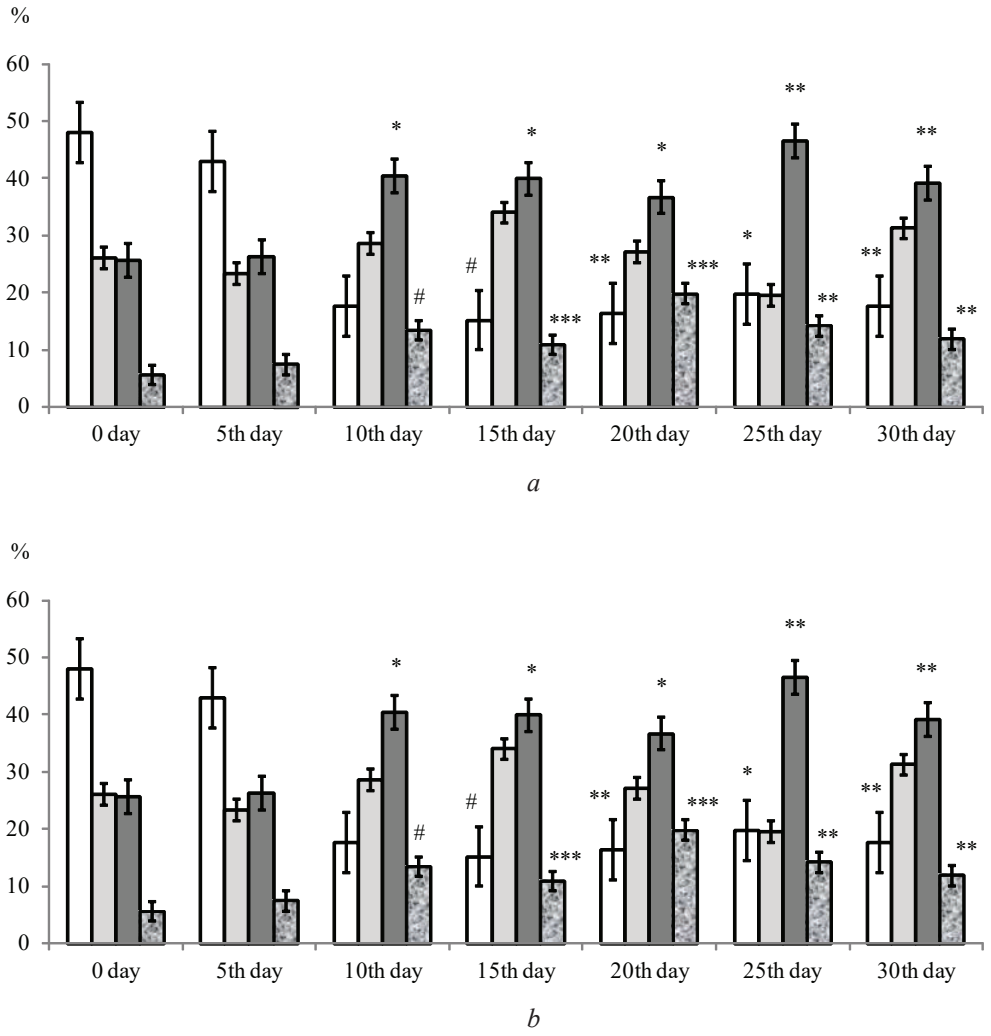

Fig. 3. Influence of intranasal administration of DA solution on dynamics of structural and functional organization of sleep in rats in the process of modeling PD: *a* – model of Parkinson's disease (control); *b* – model of Parkinson's disease+intranasal administration of DA solution; * – $p \leq 0.1$, ** – $p \leq 0.05$, *** – $p \leq 0.02$, # – $p \leq 0.01$ compared to day 0

Such changes in the period from 25 to 30 days led to a stable significant ($p \leq 0.05$) increase in the NREM3 and REM, which, combined with the complete absence of behavioral motor disorders, gives grounds to consider this phenomenon as an early manifestation of the non-motor stage of PD.

The dynamics of the structural and functional organization of sleep in animals of group II, which regularly received DA solution from day 1 after the modeling of neurodegenerative pathology, had a similar character, also consisting in a decrease in the time of wake and an increase in the representation of slow-wave and paradoxical sleep (**Fig. 2, *b***). However, the changes recorded from the 15th day of observation in the form of a trend ($p \leq 0.1$) to a reduction in the wakefulness phase (by 62 %) and an increase in the average duration of REM (by 125 %), compared with group I, indicated a slowdown in the development of nigrostriatal insufficiency in conditions for the development of experimental PD.

Under the influence of daily intranasal administration of DA, the reduction in wake in combination with an increase in the representation of superficial slow sleep (NREM1) reached the level of significant significance by day 25 ($p \leq 0.05$) (**Fig. 3, *b***). In the process of further chronization of the model, by day 30, the most pronounced changes in the representation of NREM3 (45 %) and REM (18 %) compared to zero days (32 % and 8 %, respectively), as well as the maximum decrease to 10 % ($p \leq 0.05$) of the share of wake, in contrast to 39 % in the background (**Fig. 2, *b***).

It is noteworthy that such effects of exogenous DA administration persisted even after its 5 day cessation, which was confirmed by significantly significant indicators on the 35th day after cpSN injury (**Fig. 3, *b***) and indicated a prolonged nature of the effects of intranasal DA delivery to the brain under conditions of PD modeling.

In the control group that received intranasal solvent, there were changes in the cyclic organization of sleep in the form of a predominance of its incomplete cycles by the 30th day of the study (**Fig. 4, *a***), which, obviously, was also a characteristic sign of the development of non-motor manifestations of neurodegenerative pathology under conditions of PD modeling, leading to a reduction in the number of dopamine-producing neurons and a decrease in the content of DA in the caudate nucleus and blood plasma.

In animals that received DA solution, on the contrary, there was a significant (by 76 %) decrease in the number of incomplete cycles, which stably remained at the level of 13 % to 20 % up to 30 days of observation (**Fig. 4, *b***), against the background of a significant hyperproduction of deep slow-wave and paradoxical sleep, which testified in favor of a qualitative normalization of the wake-sleep cycle due to the preventive orientation of the corrective effects of transnasal chronic administration of DA.

These indicators are supplemented by sleep cyclograms, which convincingly demonstrate a certain therapeutic potential of intranasal administration of DA to the brain, probably associated with the activation of compensatory processes aimed at slowing down neurodegeneration and the subsequent development of its clinical manifestation (**Fig. 5**, **6**).

Thus, this study is devoted to the study of neurophysiological features of the structural and functional organization of sleep as early manifestations of nigrostriatal pathology, as well as their correction by intranasal administration of DA using an experimental model of the preclinical stage of PD.

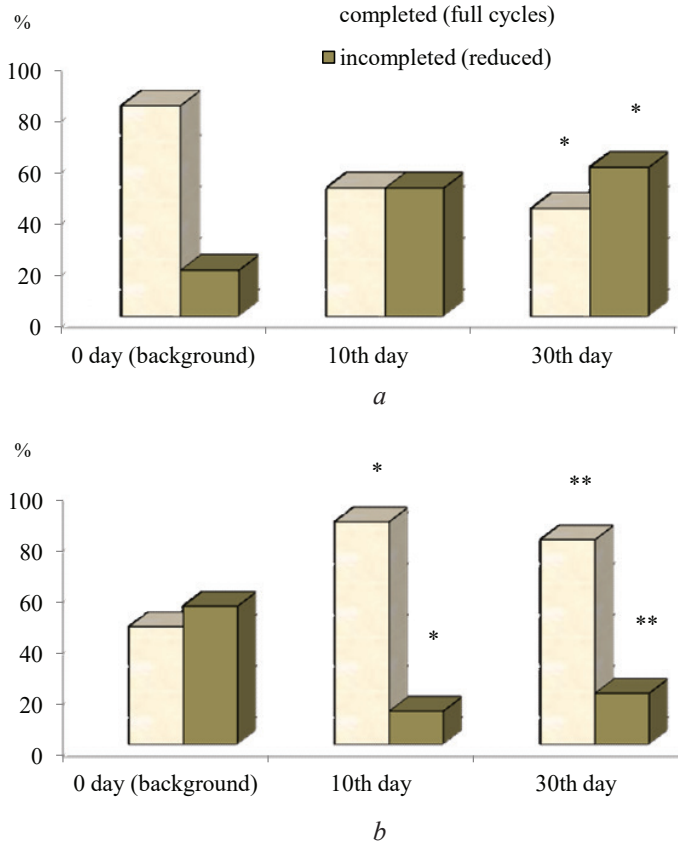

Fig. 4. Cyclic organization of sleep in the dynamics of the formation of the non-motor stage of PD: *a* – model of Parkinson's disease (control); *b* – model of Parkinson's disease with daily administration of DA solution; * – $p \leq 0.1$, ** – $p \leq 0.05$ compared to day 0

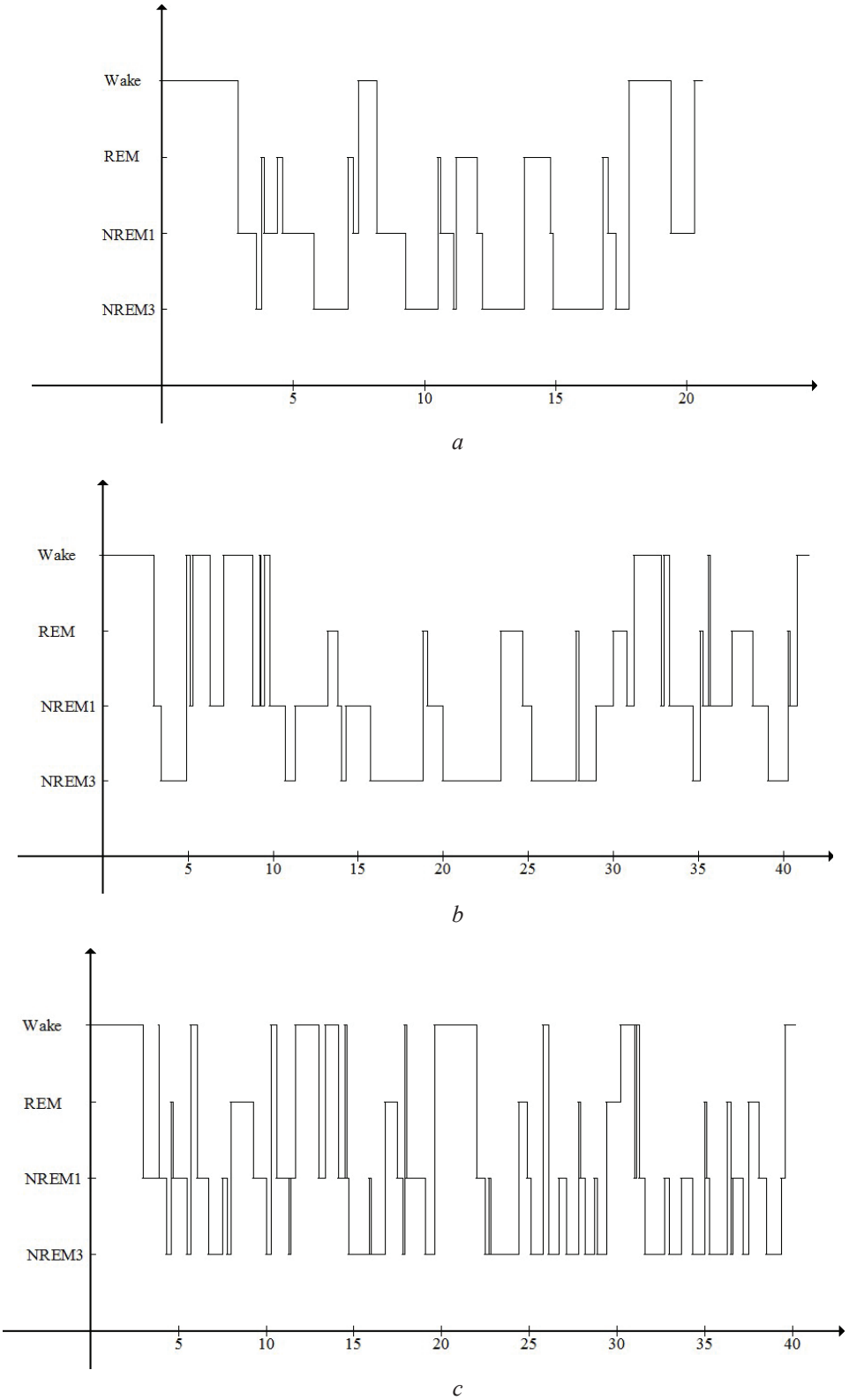

Fig. 5. Dynamics of the cyclic organization of sleep under conditions of modeling of the non-motor stage of PD in animals of group I (control: model of PD+solvent; rat No. 2): *X*-axis – sleep duration, minutes; *Y*-axis – phases and stages of sleep; *a* – 0 day (background); *b* – 10th day; *c* – 30th day; scale – 5=400 seconds

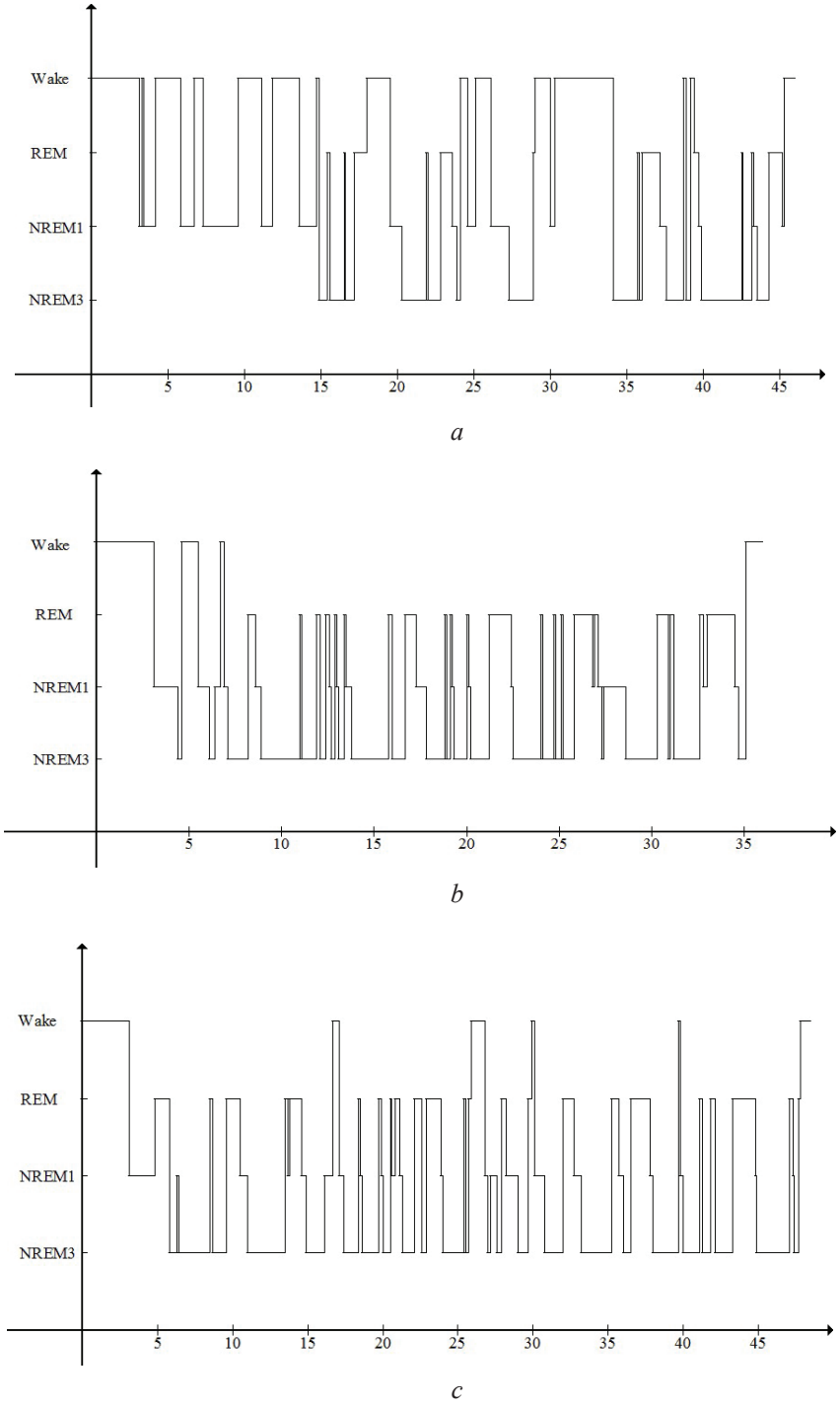

Fig. 6. Influence of chronic intranasal administration of DA on the dynamics of cyclograms under conditions of modeling of the non-motor stage of PD in animals of group II (model of PD+DA; rat No. 7): *X*-axis – sleep duration, minutes; *Y*-axis – phases and stages of sleep; *a* – 0 day (background); *b* – 15th day; *c* – 30th day; scale – 5=400 seconds

As a result of a comparative analysis of the qualitative and quantitative indicators of sleep during the formation of the non-motor stage of PD, including under the influence of exogenous administration of DA, a similar pattern of their dynamics was revealed in both groups. However, the intensity of changes was less pronounced in animals that regularly received DA, which could be due to a certain corrective

(protective) effect of its influence due to stimulation of dopaminergic receptors by subtherapeutic doses of the agonist as a result of transnasal delivery to the brain via axonal transport mechanisms [29, 43, 44]. This was most clearly demonstrated in relation to the total indicators of sleep and wake, reflecting the general trends in the formation of the non-motor stage of PD in the form of a combined increase in the representation of deep slow (NREM3) sleep and paradoxical (REM) sleep.

Significant differences in the organization of the wake-sleep cycle obtained from each experimental animal in the initial state and during the formation of neurodegenerative pathology, together with the dynamics of regressing behavioral manifestations of motor disorders associated with cpSN injury, give grounds to consider a combined increase in representation of deep slow sleep and paradoxical sleep as early manifestations of nigrostriatal insufficiency at the preclinical stage of its development (or predictors of PD), which demonstrates the adequacy of this model using laboratory rats. Our data on moderate the protective effect of course transnasal administration of DA on the structural and functional organization of the wake-sleep cycle in the conditions of the formation of nigrostriatal insufficiency may indicate the promise of the approach used to treat the early stages of PD.

As study limitations, it is possible to note the lack of correlations with the main pathomorphological and neurochemical signs of the preclinical stage of PD, which is a large autonomous study that is beyond the scope of this article. In addition, it is of interest to use other modern animal models: using systemic administration of low doses of MPTP neurotoxin (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) or dysfunction of the ubiquitin-proteasome system of the brain by intranasal administration lactacystin.

The results of this study may contribute to a detailed study of the pathogenetic mechanisms of nigrostriatal insufficiency predictors preceding the development of the clinical stage of PD.

This makes it prospects for further research in the direction of stimulating the compensatory mechanisms of the CNS and developing methods for the preventive therapy of neurodegenerative diseases.

4. Conclusion

Under the conditions of PD modeling, changes in the cyclic organization of sleep in the form of an increased number of incomplete cycles against the background of a significant hyperproduction of slow-wave and paradoxical sleep phases are early manifestations of nigrostriatal insufficiency at the preclinical stage of its development. Normalization of the qualitative characteristics of the wake-sleep cycle as a result of a course of intranasal administration of DA at a dose of 3 mg/kg, characterized by a significant (by 76 %) decrease in the number of reduced cycles, reflects the preventive focus of its effects, which may indicate a certain therapeutic potential of transnasal delivery of DA to the brain aimed at slowing down the processes of neurodegeneration and possible delaying the development of its clinical manifestation.

Conflict of interest

The authors of this study confirm that the research and publication of the results were not associated with any conflicts regarding commercial or financial relations, relations with organizations and/or individuals who may have been related to the study, and interrelations of co-authors of the article.

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