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THE EFFECT OF DIFFERENT DOSES OF LIPOPOLYSACCHARIDE ON THE DEGREE OF MORPHOLOGICAL CHANGES IN THE NIGROSTRIAL SYSTEM

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ВЛИЯНИЕ РАЗЛИЧНЫХ ДОЗ ЛИПОПОЛИСАХАРИДА НА СТЕПЕНЬ НЕЙРОДЕГЕНЕРАТИВНЫХ ИЗМЕНЕНИЙ НИГРОСТРИАЛЬНОЙ СИСТЕМЫ

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Реферат.

Точная этиология болезни Паркинсона (БП) до сих пор не ясна. Липополисахарид (ЛПС) является органическим компонентом загрязнения воздуха, но также используется для развития паркинсонического синдрома у лабораторных животных.

Цель исследования: изучить влияние различных доз интраназального ЛПС (1, 10, 100 мкг/мл) на степень морфологических признаков нейродегенерации на модели ЛПС-индуцированной БП у крыс.

Материал и методы исследования. Лабораторные животные – 4 группы, n=7 в каждой группе. Липополисахарид *Escherichia coli* или апирогенный физиологический раствор вводили интраназально в объеме 50 мкл в течение 21 дня. Морфологию выполнял заслепленный специалист. Рассчитывали процент измененных нейронов от общего числа нейронов.

Результаты исследования. Через 1 месяц после начала инстилляции ЛПС во всех трех дозах вызывал одинаковые морфологические изменения ($p>0,05$).

Выводы. Мы предполагаем, что формирование и развитие нейродегенеративных изменений нервной системы происходит по принципу «все или ничего».

Ключевые слова: липополисахарид (ЛПС); паркинсонический синдром; интраназальное введение; нигростриатная морфология; принцип «все или ничего».

Abstract.

The exact etiology of Parkinson’s disease is still unclear. Lipopolysaccharide (LPS) is an organic component of air pollution

and used also to produce parkinsonian syndrome at laboratory animals.

Objective: to investigate the effect of different doses of intranasal LPS (1, 10, 100 μg/ml) on the degree of morphological signs of neurodegeneration at LPS-induced PD model in rats.

Material and methods. Laboratory animals – 4 groups, n=7 at each group. *Escherichia coli* lipopolysaccharide or pyrogen-free saline were administered intranasally in a volume of 50 μl within 21 days. Morphology was done by blinded specialist. The percentage of changed neurons to the total number of neurons was calculated.

Results. A month after the start of the instillation LPS at all three doses caused the same morphological changes ($p>0.05$).

Conclusions. We assume that the formation and development of neurodegenerative changes in the nervous system occurs according to the principle «all or nothing».

Key words: lipopolysaccharide (LPS); parkinsonian syndrome; intranasal administration; nigrostriatal morphology; «all or nothing» principle.

Introduction. Parkinson disease (PD) is an age dependent neurodegenerative disease characterized by an irreversible progressive course and an absence of effective methods of treatment [15]. The exact etiology of PD is still unclear [6]. The loss of dopaminergic (DA) neurons in the substantia nigra (SN) is the main pathological hallmark of PD [16]. The pathogenesis and clinical manifestations of PD may be the result of complex interactions of general aging of human body with other factors leading to neurotransmitter deficiency [3, 9, 10]. There are no doubts about deleterious effects of air pollution on human health. But only a higher risk of PD among women and never smokers with exposures to high levels of airborne particulate matter <2.5 μg/m (PM 2.5) and <10 μg/m (PM 10), without any statistically significant association between ambient air pollution and PD risk, was revealed [5]. Current knowledge regarding to mechanisms of pathogenesis of PD is obtained from studies on animal models of parkinsonian syndrome caused by toxins, inflammatory agents or genetic changes. However, none of the existing models reproduce completely the complexity of the pathogenesis of PD, especially in relation to the chronic progressive process of neurodegeneration [7] and its connection with

neuroinflammation. Lipopolysaccharide (LPS) is an organic component of air pollution. According to available data the dose of LPS taken by intranasal (i/n) administration for the formation of parkinsonian syndrome is 10 μg [14**Ошибка! Источник ссылки не найден.**]. It is not clear, whether there are differences in severity of degenerative changes in the nervous system with the use of different doses of Escherichia coli LPS.

Objective: to study the effect of different dosage regime of intranasal LPS (1, 10, 100 μg/ml) on the degree of morphological signs of neurodegeneration in rats.

Material and methods. Experiments were conducted on male rats weighing 230-280 g (n=28). Animals were kept in standard vivarium conditions (12/12-hour rhythm of illumination and darkness, air temperature at 23±1°C) with free access to water and food. All manipulations with animals were made taking into account the recommendations of the European Convention on the Humane Treatment of Laboratory Animals [8]. The study was approved by the local ethics committee.

Escherichia coli lipopolysaccharide (LPS, 0111: B4, List Biological Laboratories, Campbell, CA; lot no. LPS-25E, concentration 1,10,100 mg/ml), pyrogen-free saline (PFS, Abbott Laboratories North Chicago, IL 6006, lot Nº 18 -379-DK. Expiration date until 2020) was administered intranasally (i/n) in a volume of 50 μl, 25 μl into each nasal cavity within 21 days. Based on the tasks, 4 groups of animals were formed:

• Group 1 – daily at 9.00 pyrogen-free physiological solution instilled i/n (n=7);

• Group 2 – daily at 9.00 LPS applied i/n at a dose of 1 μg / kg ml (n=7);

• Group 3 – daily at 9.00 LPS was administered i/n at a dose of 10 μg / kg/ml (n=7).

• Group 4 – daily at 9.00 LPS was instilled i/n at a dose of 100 μg/kg / ml (n=7).

The monitoring of animal activity and visual changes in motor activity was done daily by blinded specialist. Morphological examination of biological material (brain) was carried out at all animals of each group after decapitation. It was done after 7 days after the end of the introduction of LPS or physiological solution.

Morphology was done by blinded specialist too. To morphological examination, the non-fixed brain after deep freezing (to exclude artifacts) was placed on a cryostat unit. Cuts of brain thickness of 7 microns were prepared on a microtome-cryostat HM 525 (manufactured by Microm, Germany). The level of sections was determined by stereotactic atlas of rat's brain [17]. Frontal sections containing striatum were made at a level of -1.20 – -1.40 mm from bregma, containing the substantia nigra – from -5.40 to -5.80 mm from bregma. For light-optical studies, sections were stained with thionin and methylene blue according to Nissl and hematoxylin-eosin. Microscopic studies and micrographs were made using an Altami LUM-1 microscope with a digital camera and software with an increase of 40x objective.

Data processing based on determine the severity of neuronal damage and the volume of their damage. To do this, we calculated the percentage of changed neurons to the total number of neurons, according to morphometric method [0]. The counting process takes into account not only modified and unchanged neurons which are fully represented in the field of view, but also their tangential sections and fragments, in which the nuclei did not fall. Reasonably accurate information was obtained by calculating 3 fields of view. Knowing the number of distinct groups of neurons, determine the percentage ratio of modified neurons and the total number of neurons in this area. All morphological data were expressed as the median [25^{th} percentile; 75^{th} percentile]. Multiple comparisons were analyzed by Kruskal-Wallis test and by Mann-Whitney test. $p<0.05$ was considered statistically significant. All statistical analyzes were performed with Statistica v 6.0 (StatSoft Inc.).

Results and discussion. A month after the start of the instillation, there were no differences in the characteristics of the motor activity of the main and control rats. During the entire experiment no death of animals was recorded. Morphological data. In the rats of the control group, the introduction of water for injection did not lead to pronounced structural changes in the nigrostriatal system of the rat brain. In the substantia nigra of rat's brain, no gross structural changes in the neurons were detected. Norm-chromic cells of a symmetric shape with a uniformly distributed tigroid substance prevailed. Their nuclei had a rounded shape, with large nucleoli,

usually located in the center of the nucleus. In small numbers, hyperchromic and hypochromic neurons were detected. In separate fields of view single neurons with tigrolysis were encountered. A similar pattern was observed in the region of the basal nuclei (Figure 1).

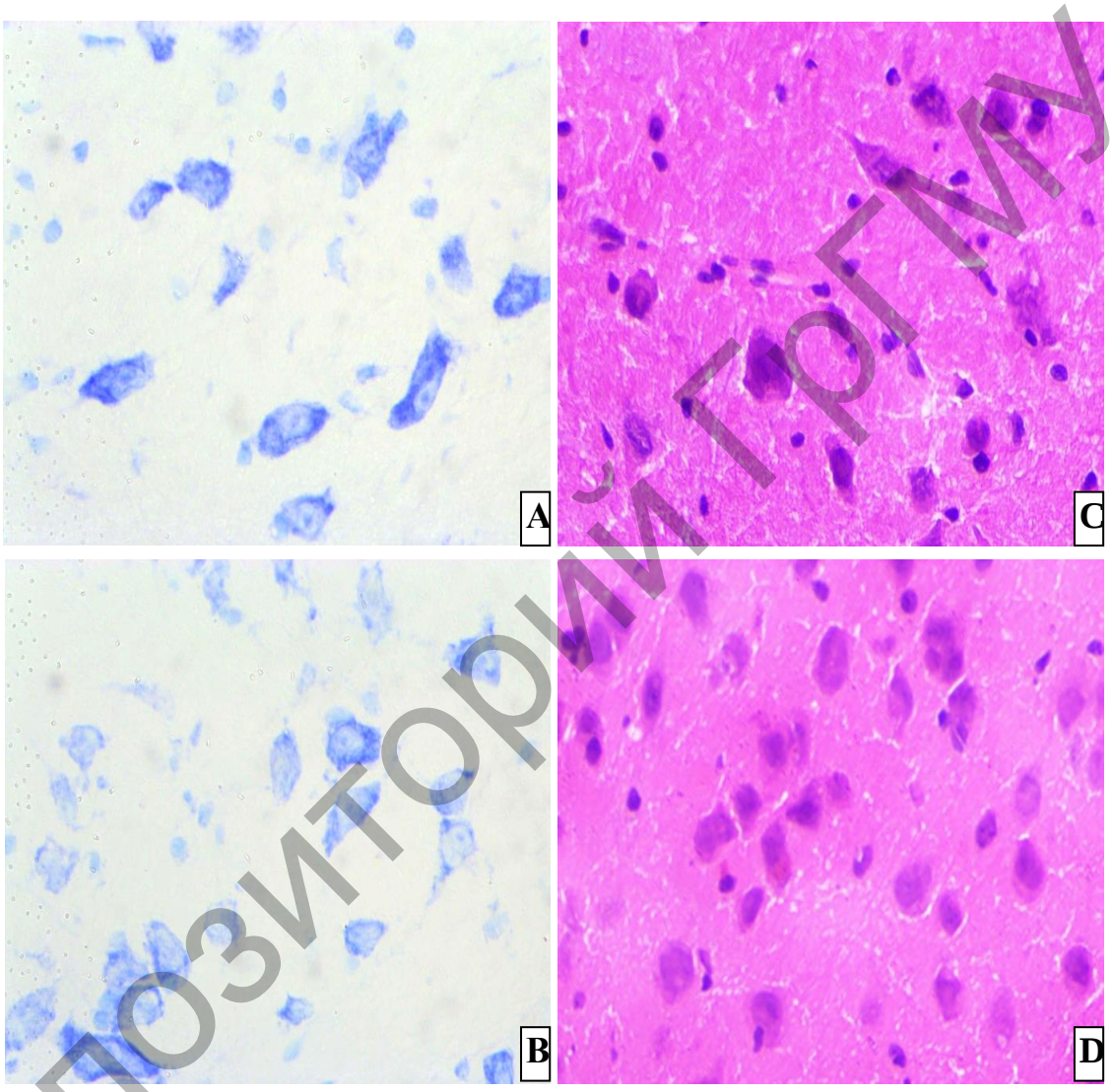

Figure 1. – Microphoto frontal sections of the substantia nigra (A, C) and striatum (B, D) of the rat brain after the injection of the solvent Color: according to Nissl (A, B), hematoxylin-eosin (C, D). Magnification: x 400

Significant changes in histostructure were observed in the compact part of the substantia nigra after the intranasal administration of LPS at a dose of 1 μg/kg/ml. Most neurons had some signs of neurodegeneration. Vacuolization of the nucleus and cytoplasm of nerve cells was detected. Tigrolysis of neurons was noted. Near

destructively altered neurons, small clusters of glial cells were detected. The glial index was 3.10.

Neurodegenerative changes were observed in the striatum. Most of the neurons were hypochromic, the nucleus and the nucleolus were not detected in them. In some parts of the striatum, pericellular edema begins to develop. A slight increase in the number of glial elements was noted (Figure 2).

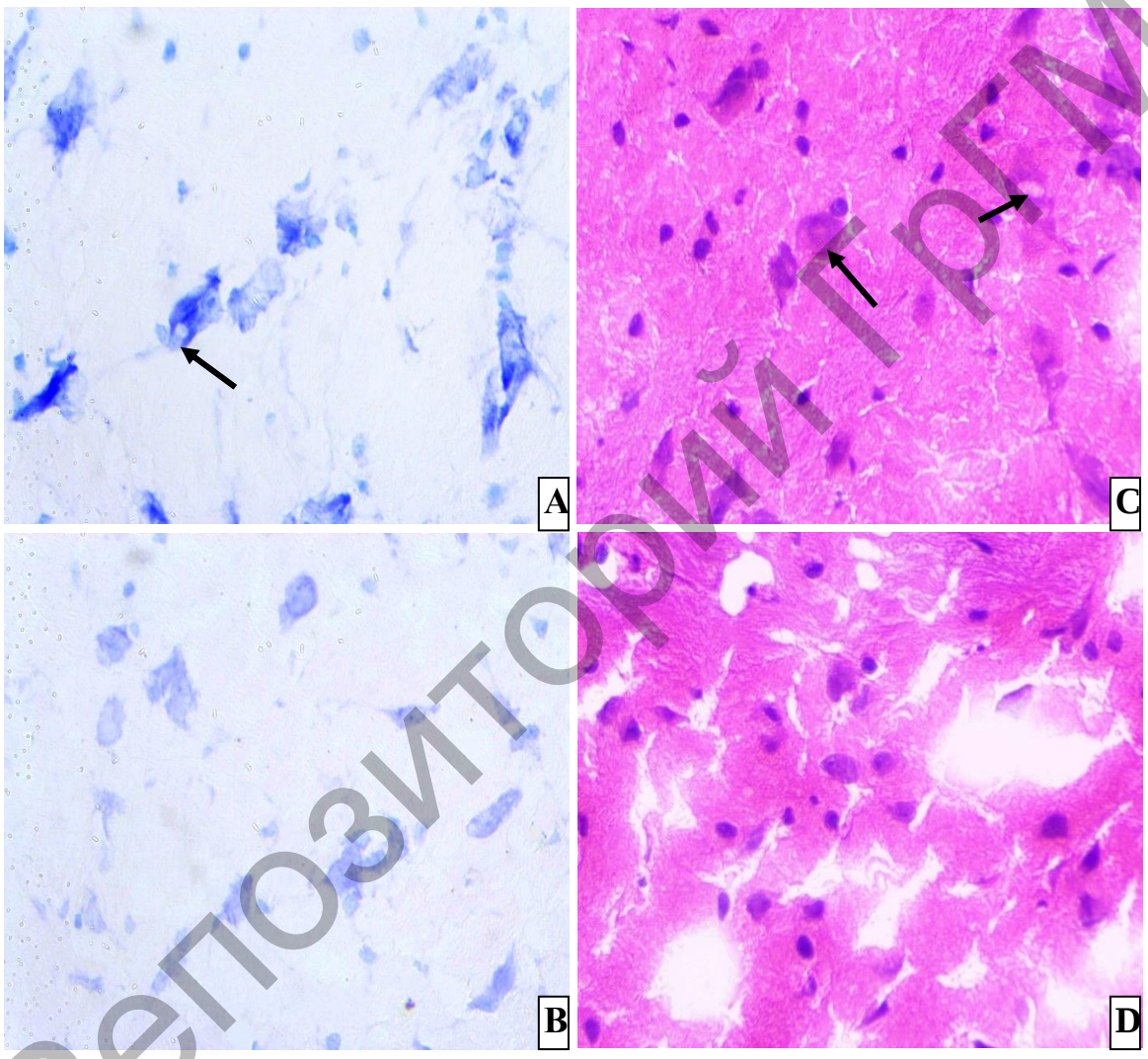

Figure 2. – Microphoto frontal sections of the substantia nigra (A, C) and striatum (B, D) after intranasal administration of LPS at a dose of 1 μg/kg ml. Arrows – vacuoles.
Color: according to Nissl (A, B), hematoxylin-eosin (C, D). Increase: x 400

In the substantia nigra of the rat brain after intranasal administration of LPS at a dose of 10 μg/kg/ml, along with normochromic neurons with a nucleus and nucleolus, a significant

number of hypochromic and hyperchromic cells were found. Observed vacuolization of nuclei and cytoplasm of nerve cells, partial tigrolysis. Single cytoplasmic inclusions of the Lévy type were detected. The number of glial cells is moderately increased. The glial index is 3.09.

In the region of the basal nuclei most of the neurons retained their normal structure. They are normochromic, with a centrally located nucleus with a nucleolus. Some cells are hypochromic, sometimes with impaired tinctorial properties (Figure 3).

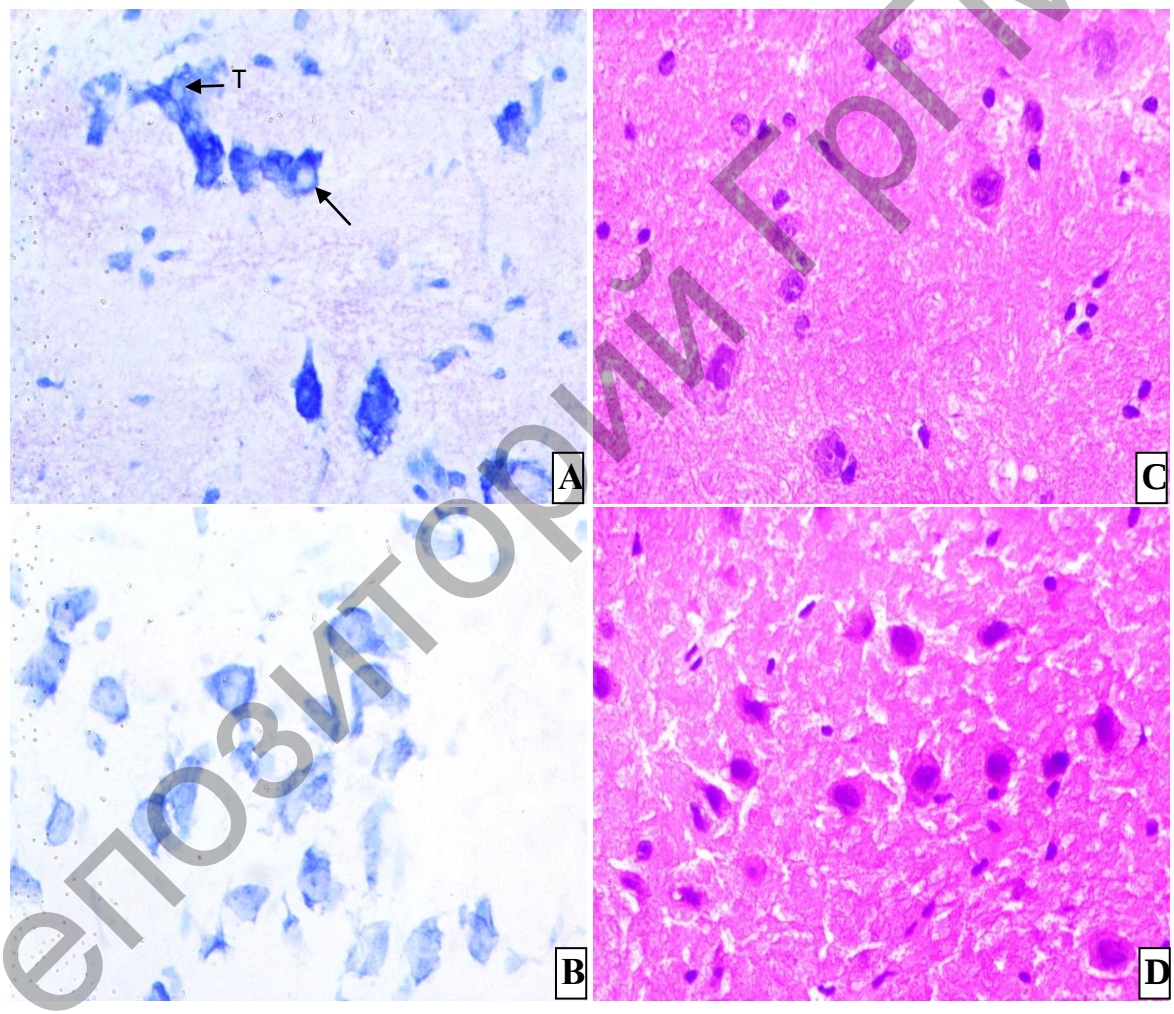

Figure 3. – Microphoto frontal sections of the substantia nigra (A, C) and striatum (B, D) after intranasal administration of LPS at a dose of 10 μg/kg/ml. Arrows – vacuoles.
Color: according to Nissl (A, B), hematoxylin-eosin (C, D). Increase: x 400

In the substantia nigra of the rat brain after administration of LPS at a dose of 100 μg/kg, along with normochromic neurons in which the nucleus is clearly defined, hypochromic and hyperchromic cells are observed, often with large vacuoles in the cytoplasm. Most of the nerve cells are affected by tinctorial properties. There is partial tigrolysis. There were a few cytoplasmic inclusions such as Lewy bodies. The number of glial cells is slightly increased. The glial index is 3.46 (Figure 4).

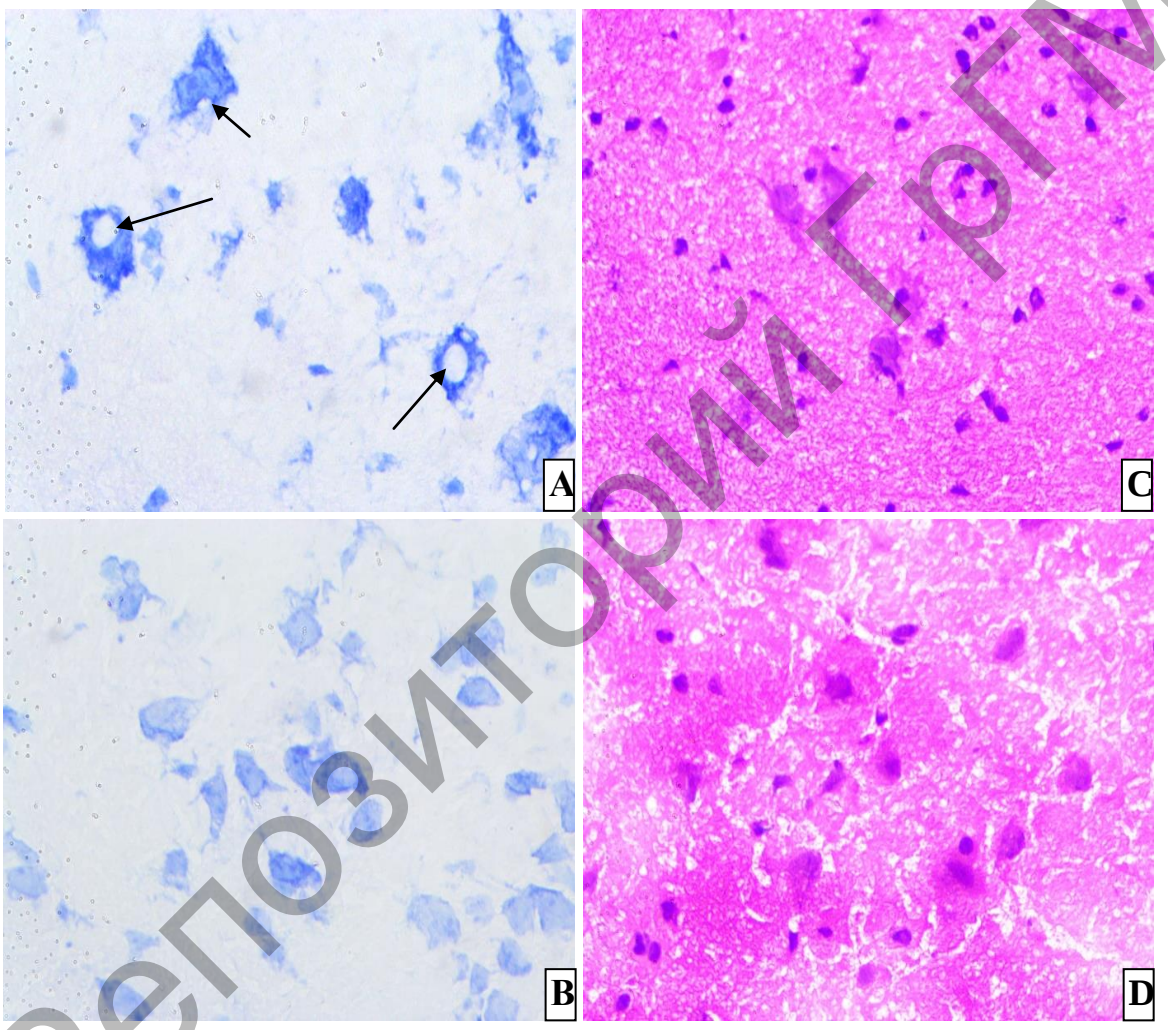

Figure 4. – Microphoto frontal sections of the substantia nigra (A, C) and striatum (B, D) after intranasal administration of LPS at a dose of 100 μg/ kg/ml. Arrows – vacuoles.
Color: according to Nissl (A, B), hematoxylin-eosin (C, D).
Increase: x 400

Table 1. – Modified and unchanged neurons of the substantia nigra and basal ganglii after 21 days of intranasal administration of LPS at doses of 1, 10, 100 μg/ml.

	Substantia nigra				Basal ganglia			
	UN	WN	GN	MN	UN	WN	GN	MN
LPS 1, n=7	6 [5; 7]	15 [15; 17]	16 [15; 18]	12 [11; 13]	14 [11; 15]	14 [12; 15]	14 [13; 15]	9 [7; 10]
LPS 10, n=7	6 [5; 7]	16 [15; 17]	17 [16; 18]	11 [10;13]	14 [13; 16]	16 [15; 17]	12 [11;13]	8 [7; 9]
LPS 100, n=7	6 [4; 7]	15 [14; 17]	18 [16; 19]	10 [9; 13]	10 [9;14]	18 [16; 19]	13 [11; 14]	10 [9;12]
Kruskal-Wallis test	H (2, N=21) =,547973 p=,7603	H (2, N= 21) =1,602344 p=,4488	H (2, N=21) =3,207713 p=,2011	H (2, N=21) =2,670389 p=,2631	H (2, N=21) =5,079996 p=,0789	H (2, N= 21) =10,17893 **p=,0062**	H (2, N= 21) =4,359195 p=,1131	H (2, N= 21) =6,110190 **p=,0471**

In the region of the basal nuclei, along with normochromic, both hypochromic and hyperchromic neurons were detected. In most cells, the nucleus with the nucleolus was not determined, sometimes the nucleus was shifted to the periphery of the cell. A violation of the tinctorial properties of neurons was noted. In some areas, pericellular edema was observed.

Table 1 presents data on modified and unchanged neurons of the substantia nigra and basal ganglii after 21 days of intranasal instillation of lipopolysaccharide (1, 10, 100 μg/kg/ml) and statistical analysis results.

The obtained data demonstrate statistically significant differences between groups in terms of number of weakly modified neurons (WN) and shadow cells, missing neurons (MN) at basal ganglii. But we do not observe a decrease in the number of unchanged neurons and/or an increase in the number of altered neurons associated with an increase in the dose of LPS at intranasal administration. Table 2 presents data on the degree of damage of the neurons of the substantia nigra and basal ganglii after 21 days of intranasal instillation of lipopolysaccharide (1, 10, 100 μg/kg/ml) and statistical analysis results.

The obtained at table 2 data does not demonstrate statistically significant differences between groups. It is possible that initial differences identified at table 1 were lost in the subsequent mathematical processing of digital data. Also, looking at numerical values we do not observe any dynamics of the degree of neuronal damage associated with an increase in the dose of LPS at intranasal administration. There were statistically significant differences between every LPS groups and control group ($p<0.05$).

Our data suggest that there is no straight line relationship between the dose of LPS and the degree of structural changes. Most likely the development of morphological changes under the influence of LPS occurs on the principle of «all or nothing». «All-or-nothing» nature has important implications for signalling in nervous system [0].

Table 2. – The degree of damage to the neurons of the substantia nigra and basal ganglii after 21 days of intranasal administration of LPS at doses of 1, 10, 100 μg/ml.

	Substantia nigra			Basal ganglia		
	severity of the lesion, %	volume of the lesion, %	degree of the lesion, %	severity of the lesion, %	volume of the lesion, %	degree of the lesion, %
LPS 1, n=7	57,14 [56,36; 58,33]	87,76 [87,27; 89,36]	72,45 [71,82; 73,92]	44 [41,3; 48,08]	71,43 [67,39; 78,31]	57,14 [54,36; 62,69]
LPS 10, n=7	56 [53,85; 58,33]	88,24 [86,54; 89,59]	72,12 [70,2; 73,96]	40,38 [36; 42,86]	73,08 [68; 75]	56,73 [52; 59,1]
LPS 100, n=7	58,82 [56, 60]	88 [86; 91,3]	73,47 [72; 75,49]	44 [39,22; 48,08]	80 [72,55; 83,64]	62 [55,89; 66,35]
Kruskal-Wallis test	H (2, N=21) =2,793858 p=,2474	H (2, N=21) =,2926102 p=,8639	H (2, N=21) =1,179760 p =,5544	H (2, N=21) =5,820589 p=,0545	H (2, N=21) =4,733420 p=,0938	H (2, N=21) =3,844797 p=,1463

By analogy, we assume that the formation and development of neurodegenerative changes in the nervous system (nigrostrial part) occurs according to the same principle. If the dose of LPS enters the body exceeds a threshold value (capable of causing neurodegenerative changes), then an increase in the dose of LPS does not lead to an increase in the degree of morphological changes. Therefore, it can be assumed that the introduction of doses of LPS that are below a certain threshold value will not lead to the development of morphological changes. The question remains: what factors and under what conditions can influence nigral DA neurons in the brain of rats (or other laboratory animals). And is it possible to draw a parallel with the human brain?

The mechanism of action of LPS on the body is well understood. So circulating cytokines produced by systemic inflammation, such as TNFα and IL-1β, are known to cause neuroinflammation [12, 18], neurotoxicity [12, 25] and damage to the cerebral vessels [24]. Thus, chronic inflammation associated with multiple systemic injections of low concentrations LPS leads to mild neuroinflammation in adult mice, which makes animals more susceptible to further proinflammatory damage [20]. It has been shown that the constant exposure to the proinflammatory microenvironment leads to an increased formation and release of inflammatory mediators, which interact with the age factor to impair the functional capacity of the substantia nigra pars compacta (SNC) and the locus coeruleus (LC) [2].

Clinical and morphological changes in laboratory animals under the influence of LPS have been described by a number of researchers. So the study [14] showed that prolonged i/n instillation of LPS resulted in progressive hypokinesia, selective loss of DA neurons and a decrease in DA content in the genitals, as well as α-synuclein aggregation in old mice [13]. In this research, i/n LPS instillation also induced a PD model in young and old mice. Other studies have shown that LPS leads to a significant loss of DA neurons, accompanied by the activation of microglia and the NF-kB pathway [19, 22]. All these data indicate the universality of the neuroinflammatory trigger for the formation of neurodegeneration.

The relevance of our study is determined by the importance of studying the effects of environmental toxicants on the central nervous system. It is known that environmental factors affect the central

nervous system through several cellular and molecular mechanisms [11, 21]. Studies show that these effects on the CNS are chronic, start from childhood, and may take time (years) to accumulate damage. It is possible that the effect on the nervous system of a large single dose of LPS is similar to the prolonged impact of low doses of LPS. The assumption of the cumulative effect of LPS requires further experimental verification.

Conclusion. Available data of different investigations indicates the possibility that respiratory environmental triggers can induce neuroinflammation and contribute to the development of PD in humans. We determined the same level of morphological changes in the rat's brains at different doses of LPS. It makes clear the importance of determining the minimum threshold dose of LPS that causes objective neurodegenerative neiroinflamatory changes in the brain. It is still unknown a time frame required for triggering of neurodegenerative changes from different doses of LPS. Further studies with different doses of LPS are needed to study the contribution of pro-inflammatory environmental factors to the development of not only PD, but also other neurodegenerative diseases.

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ПРЕДИКТОРЫ И ПРОГНОЗ РАЗВИТИЯ ДИСФУНКЦИИ ДЫХАТЕЛЬНОЙ МУСКУЛАТУРЫ У ПАЦИЕНТОВ С ПРОФЕССИОНАЛЬНЫМИ ЗАБОЛЕВАНИЯМИ ОРГАНОВ ДЫХАНИЯ

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PREDICTORS AND FORECAST OF THE DEVELOPMENT OF RESPIRATORY MUSCULATION DYSFUNCTION IN PATIENTS WITH OCCUPATIONAL RESPIRATORY DISEASES

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Реферат.

Проблема дисфункции дыхательной мускулатуры (ДМ) у пациентов с профессиональной патологией органов дыхания (ППОД) является актуальной в мире.