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### MORPHOMETRIC CHARACTERISTICS OF THE MAIN STRUCTURAL COMPONENTS OF THE POSTERIOR EYE WALL IN RATS UNDER THE IMPACT OF A COMPLEX OF MONOSODIUM GLUTAMATE, SODIUM NITRITE AND PONCEAU 4R

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The paper presents the results of a morphometric study of the components of the posterior wall of the rat eye under the complex effect of food additives. It has been established that the endogenous effect of the complex of sodium glutamate, sodium nitrite and Ponceau-4R causes significant morphometric changes in the structures of the retina, which proves their neurotoxic properties on retinal cells and is expressed by a progressive decrease in morphometric parameters in the chronological aspect. These changes indicate the development of degenerative changes that can affect visual functions, causing their deterioration and confirm the need to limit the consumption of food additives to reduce the risks associated with visual impairment.

**Key words:** food additives, monosodium glutamate, sodium nitrite, Ponceau 4R, retina, eye, rats.

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### МОРФОМЕТРИЧНА ХАРАКТЕРИСТИКА ОСНОВНИХ СТРУКТУРНИХ КОМПОНЕНТІВ ЗАДНЬОЇ СТІНКИ ОКА ЩУРІВ ПІД ДІЄЮ КОМПЛЕКСУ ГЛУТАМАТУ НАТРІЮ, НІТРИТУ НАТРІЮ ТА ПОНСО 4R

В роботі представлені результати морфометричного дослідження складових задньої стінки ока щурів при комплексній дії харчових добавок. Встановлено, що ендогенна дія комплексу глутамату натрію, нітриту натрію та Понсо-4R викликає значні морфометричні зміни в структурах сітківки, що доводить їх нейротоксичні властивості на клітини сітківки та виражається прогресивним зменшенням морфометричних показників в хронологічному аспекті. Дані зміни свідчать про розвиток дегенеративних змін, які можуть впливати на зорові функції, спричиняючи їхнє погіршення і підтверджують необхідність обмеження споживання харчових добавок для зниження ризиків, пов'язаних із порушеннями зору.

**Ключові слова:** харчові добавки, глутамат натрію, нітрит натрію, Понсо 4R, сітківка, око, щури.

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A wide range of chemical substances or natural compounds can be considered as food additives that are added to food products during production or storage to enhance certain qualities, such as flavor, appearance and shelf life. The use of food additives is permitted provided that, according to available scientific data, their consumption does not pose a threat to consumer health and is technologically justified [2].

The use of food additives remains a subject of significant debate within the scientific community, primarily due to the lack of comprehensive research on their impact on the human body, especially under conditions of combined exposure. Existing studies do not provide a definitive answer regarding the varying degrees of human susceptibility to the effects of food additives, and no data on their combined impact has been found to date [1]. However, it is important to acknowledge that the effect of any chemical substance on the human body depends on several factors, including individual characteristics, the quantity of the substance and the duration of exposure [7].

Our analysis of the content of food additives in domestic and foreign products revealed that the most common additives are monosodium glutamate, sodium nitrite and Ponceau 4R.

The primary excitatory neurotransmitter in the brain is glutamate, which activates specific receptors and influences both physiological and pathological processes. When monosodium glutamate is consumed, excessive stimulation of these receptors can lead to excitotoxicity. Once glutamate enters cells through the GLAST glutamate transporter, it is metabolized into the non-toxic glutamine by glutamine synthetase. Synaptic transmission between bipolar, photoreceptor and ganglion cells in the retina is facilitated by glutamic acid. However, its excessive presence can lead to neuronal death [4, 6, 10].

A review of the hazardous effect of sodium nitrite shows that this food additive can potentially be harmful to the retina, as nitrites can react with other compounds in the body, forming nitrosamines, which are known to have carcinogenic properties. Nitrosamines can have a harmful effect on cells and tissues, including the retina, although the specific impact on retinal cells has not been extensively studied [9].

Research on the impact of food colorants focused on the effect of food additives, particularly E124, on visual processing and attention in children. The study showed that food additives, including food colorants, can have a negative impact on visual attention and perception, which may indirectly affect the function of the retina. However, it is important to emphasize that the existing literature is limited, and further research is needed for a clearer understanding of the impact of E124 on the retina [13].

**The purpose** of the study was to determine the dynamics of changes in the metric parameters of the components of the posterior eye wall in rats under normal conditions and under the influence of a complex of food additives – monosodium glutamate, sodium nitrite and Ponceau 4R.

**Materials and methods.** The study was conducted on 84 sexually mature male Wistar rats. The control group, consisting of 10 rats, received drinking water and orally administered physiological saline. Rats in the experimental group, with free access to water, were given 0.6 mg/kg of sodium nitrite (Sodium nitrite E250, Uralchem, China), 20 mg/kg of monosodium glutamate (Monosodium glutamate E621, Multichem, China), and 5 mg/kg of Ponceau 4R (Ponceau 4R E124, Multichem, China) in 0.5 ml of distilled water once a day orally. The doses of food additives were half of the permissible limit in food products. The adaptive behavior of the rats was assessed using the open field test [14].

The animals were euthanized at 1, 4, 8, 12 and 16 weeks through an overdose of thiopental anesthesia. After euthanasia, fragments of the posterior eye wall were fixed in 10 % formalin solution. The pieces of the posterior eye wall were then embedded in Epon-812 and paraffin using conventional technique [11].

Sections with a thickness of 5-10  $\mu\text{m}$  were obtained using the ARM 3600 microtome. Semi-thin sections were obtained using the UNTP-7 ultramicrotome. After staining with hematoxylin and eosin, as well as methylene blue, the sections were placed in polystyrene and examined under a light microscope. Using a digital microscope with the Levenhuk D740T digital microphotography attachment and specialized software adapted for this research, microphotography and morphometric analysis were conducted. Statistical processing of the morphometric data was performed using Excel with the built-in “VGA analysis package” add-in, specifically the “descriptive statistics” tool. To test the normality of variances, the Shapiro-Wilk test was applied, and when the data followed a normal distribution, comparisons were made using the Student’s t-test for independent samples. A difference was considered statistically significant at  $p < 0.05$  [3, 8].

All animal experiments were carried out in compliance with the requirements of the European Convention for the Protection of Vertebrate Animals used for Experimental and Scientific Purposes (Strasbourg, 1986), in accordance with the rules for keeping experimental animals established by European Parliament and Council Directive (2010/63/EU) and the Order No. 134 of the Ministry of Education and Science, Youth and Sports of Ukraine as of 01.03.2012, No. 249 “On approval of the procedure for conducting tests, experiments on animals by research institutions”, as well as the recommendations of the First National Congress of Ukraine on Bioethics (2001).

**Results of the study and their discussion.** The morphometric study of the total thickness of the posterior eye wall in rats has found the average values of  $224.80 \pm 8.00 \mu\text{m}$  (Table 1) (Fig. 1).

Table 1

**Morphometric parameters of the outer layers of the posterior eye wall in rats**

Parameters	Total Thickness ( $\mu\text{m}$ )	Photoreceptor Layer (PR) ( $\mu\text{m}$ )	Outer Nuclear Layer (ONL) ( $\mu\text{m}$ )	Outer Plexiform Layer (OPL) ( $\mu\text{m}$ )
Control group	$224.80 \pm 8.00$	$26.66 \pm 1.64$	$62.47 \pm 2.00$	$12.80 \pm 0.78$
Week 1	$213.55 \pm 8.80$	$27.25 \pm 1.20$	$67.46 \pm 2.80$ *	$14.20 \pm 0.70$ *
Week 4	$202.68 \pm 9.10$ *	$27.22 \pm 1.30$	$63.93 \pm 2.10$	$14.24 \pm 0.70$ *
Week 8	$184.87 \pm 10.10$ *	$23.92 \pm 2.60$	$56.30 \pm 3.10$ **	$12.50 \pm 0.80$ **
Week 12	$174.87 \pm 10.60$ *	$21.00 \pm 2.20$ *	$47.77 \pm 3.30$ **	$11.60 \pm 0.70$
Week 16	$168.00 \pm 12.90$ *	$19.90 \pm 2.00$ *	$43.20 \pm 4.40$ *	$10.22 \pm 1.10$ *

Notes: \* –  $p < 0.05$  compared to the control group; \*\* –  $p < 0.05$  compared to the previous observation period.

On week 1 of the experiment, consumption of complex of food additives resulted in an insignificant increase in the average values, which amounted to  $213.55 \pm 8.80 \mu\text{m}$  ( $p < 0.05$ ).

On week 4 of the experiment, consumption of the complex of monosodium glutamate, sodium nitrite and Ponceau 4R led to a decrease in the average values, which amounted to  $202.68 \pm 9.10 \mu\text{m}$ . These values were not significantly different from the values of the previous term of study, though they were by 9.84 % significantly lower compared to the control group values ( $p < 0.05$ ).

On week 8 of the experiment, the average values did not differ significantly from the values at week 4 of the experiment and amounted to  $184.87 \pm 10.10 \mu\text{m}$ . However, they were by 17.76 % significantly lower than the values in the control group of animals ( $p < 0.05$ ).

On week 12 of consumption of monosodium glutamate, sodium nitrite and Ponceau 4R, the average thickness values of the posterior wall of the eye were  $174.87 \pm 10.60 \mu\text{m}$ . These values did not differ significantly from those of the previous term of observation but were by 22.21 % significantly lower compared to the values in the control group of animals ( $p < 0.05$ ).

On week 16 of the experiment, the average thickness values of the posterior wall of the eye were  $168.00 \pm 12.90 \mu\text{m}$ , which did not differ significantly from the values at week 12 of consuming monosodium glutamate, sodium nitrite and Ponceau 4R. However, these values were by 25.27 % significantly lower compared to the control group ( $p < 0.05$ ).

Morphometric analysis of the posterior wall of the rat eye revealed that the thickness of the photoreceptor layer in the control group was  $26.66 \pm 1.64 \mu\text{m}$ .

The consumption of the complex of food additive did not result in significant changes in morphometric parameters up to week 12 of the experiment, as they did not differ significantly from the results of previous term of study or from the values in the control group of rats.

On week 12, the effect of the chemical compound complex led to a significant decrease in the average thickness of the photoreceptor layer of the retina in rats by 21.23 % compared to the control group values, which did not significantly differ from the results of the previous term of study ( $p < 0.05$ ).

On week 16 of the experiment, the average thickness of the photoreceptor layer of the retina in rats was  $19.90 \pm 2.00 \mu\text{m}$ , which did not significantly differ from the results of the previous term of the experiment, but was by 25.36 % significantly lower than the control group values ( $p < 0.05$ ) (Fig. 2).

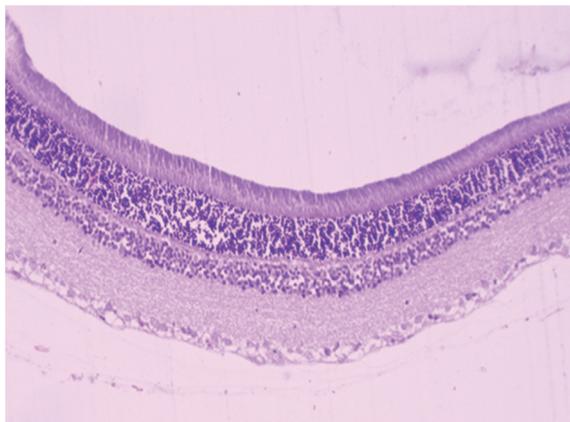


Fig. 1. Retina of the eye in the control group of rats. H&E stain. Ocular lens: 10×magnification. Objective lens: 10×magnification.

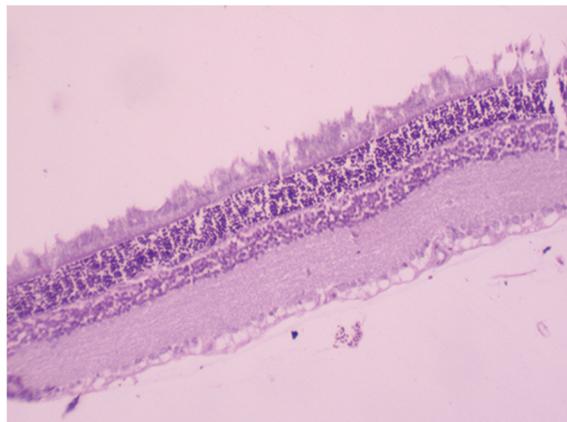


Fig. 2. Degenerative changes in the photoreceptor layer of the retina of rats on week 16 of consuming the complex of food additives. H&E stain. Ocular lens: 10×magnification. Objective lens: 10×magnification.

Morphometric analysis of the posterior wall of the eye revealed that the average thickness of the outer nuclear layer of the retina in the control group of rats was  $62.47 \pm 2.00 \mu\text{m}$ .

Consumption of food additives showed that the average values of the outer nuclear layer on week 1 were  $67.46 \pm 2.80 \mu\text{m}$ , which was by 7.99 % significantly greater compared to the control group values. On week 4, the values were  $63.93 \pm 2.10 \mu\text{m}$ , and they did not significantly differ from the results of the control group of rats or from the average values of previous term of the experiment ( $p < 0.05$ ).

On week 8 of the experiment, the average thickness of the outer nuclear layer was  $56.30 \pm 3.10 \mu\text{m}$ , which was by 11.93 % significantly lower than the values on week 4, and by 9.88 % significantly lower than the control group values ( $p < 0.05$ ).

By week 12, the consumption of monosodium glutamate, sodium nitrite and Ponceau 4R led to a decrease in the average thickness of the outer nuclear layer of the rat retina by 15.29 % compared to the previous term, which amounted to  $47.77 \pm 3.30 \mu\text{m}$ . This value was also by 23.53 % significantly lower than the control group values ( $p < 0.05$ ).

On week 16 of the experiment, the average thickness of the outer nuclear layer of the rat retina was  $43.20 \pm 4.40 \mu\text{m}$ , which did not significantly differ from the results of the previous period of study. However, it was by 30.85 % significantly lower compared to the control group ( $p < 0.05$ ).

Morphometric analysis of the posterior wall of the eye revealed that the outer plexiform layer of the retina in the control group of rats was  $12.80 \pm 0.78 \mu\text{m}$ .

Consumption of the complex of food additives revealed that the average values of the outer plexiform layer on week 1 were  $14.20 \pm 0.70 \mu\text{m}$ , which was by 10.94 % significantly greater than the

control values. On week 4, the values were  $14.24 \pm 0.70 \mu\text{m}$ , which did not significantly differ from the results of the previous term of the experiment but were by 11.25 % significantly greater compared to the results of the control group ( $p < 0.05$ ).

On week 8 of the experiment, the thickness of the outer plexiform layer was  $12.50 \pm 0.80 \mu\text{m}$ , which was by 13.52 % significantly lower compared to the average values on week 4, and did not significantly differ from the control group values ( $p < 0.05$ ).

By week 12, consumption of pollutants led to insignificant decrease in the average thickness of the outer plexiform layer of the rat retina, amounting to  $11.60 \pm 0.70 \mu\text{m}$  ( $p < 0.05$ ). On week 16 of the experiment, the average thickness of the outer plexiform layer of the rat retina was  $10.22 \pm 1.10 \mu\text{m}$ , which did not significantly differ from the results of the previous period, but was by 20.15 % significantly lower compared to the control group ( $p < 0.05$ ).

The morphometric study of the retina in the control group of rats revealed that the thickness of the inner nuclear layer was  $44.14 \pm 2.72 \mu\text{m}$  (Table 2).

Table 2

**Morphometric parameters of the inner layers of the posterior wall of the rat eye**

Parameters	Inner nuclear layer (INL) ( $\mu\text{m}$ )	Inner plexiform layer (IPL) ( $\mu\text{m}$ )	Ganglion cell layer (GL) ( $\mu\text{m}$ )
Parameters	$44.72 \pm 2.28$	$58.05 \pm 2.24$	$24.89 \pm 2.00$
Control group	$48.28 \pm 2.60$	$50.89 \pm 2.60$ *	$28.42 \pm 3.30$
Week 1	$46.11 \pm 1.20$	$50.46 \pm 2.10$ *	$27.26 \pm 1.00$ *
Week 4	$42.10 \pm 3.00$	$48.70 \pm 1.80$ *	$22.00 \pm 1.60$ **
Week 8	$32.53 \pm 2.30$ * **	$40.89 \pm 2.60$ * **	$20.97 \pm 1.30$ *
Week 12	$32.72 \pm 3.20$ *	$40.38 \pm 3.60$ *	$21.55 \pm 1.80$

Notes: \* –  $p < 0.05$  compared to the control group; \*\* –  $p < 0.05$  compared to the previous observation period.

On week 1, 4 and 8 of the consumption of monosodium glutamate, sodium nitrite and Ponceau 4R, the average values of the inner nuclear layer were  $48.28 \pm 2.60 \mu\text{m}$ ,  $46.11 \pm 1.20 \mu\text{m}$ , and  $42.10 \pm 3.00 \mu\text{m}$ , respectively. These values did not significantly differ from the results of previous time periods of the experiment or from the control group values ( $p < 0.05$ ).

The impact of the chemicals at week 12 resulted in a 22.73 % decrease in the average thickness of the inner nuclear layer of the rats' retinal wall compared to the previous observation period, amounting to  $32.53 \pm 2.30 \mu\text{m}$ . This value was by 26.30 % significantly lower compared to the control group ( $p < 0.05$ ).

On week 16 of the experiment, the average thickness of the inner nuclear layer of the rats' retinal wall was  $32.72 \pm 3.20 \mu\text{m}$ , which did not significantly differ from the results of the previous term of the experiment. However, it was by 25.87 % significantly lower compared to the control group values ( $p < 0.05$ ).

The morphometric study of the posterior wall of the eye revealed that the average thickness of the inner plexiform layer of the rats' retina was  $58.05 \pm 2.24 \mu\text{m}$  in the control group.

On week 1 of consumption of the complex of food additives the average thickness of the inner plexiform layer was  $50.89 \pm 2.60 \mu\text{m}$ , which was by 12.33 % significantly lower compared to the control group values. On week 4 of the experiment, it measured  $50.46 \pm 2.10 \mu\text{m}$ , which was by 13.07 % significantly lower than the control group values. On week 8, it was  $48.70 \pm 1.80 \mu\text{m}$ , which represented a significant decrease by 16.11 % compared to the control values and did not differ from the previous term of the experiment ( $p < 0.05$ ).

On week 12, consumption of the complex of monosodium glutamate, sodium nitrite and Ponceau 4R led to a decrease in the average thickness of the inner plexiform layer of the rat retina by 16.04 % compared to the previous period of the study, amounting to  $40.89 \pm 2.60 \mu\text{m}$ . These values were by 29.56 % significantly lower compared to the control group ( $p < 0.05$ ).

On week 16 of the experiment, the average thickness of the inner nuclear layer of the posterior eye wall in rats was  $40.38 \pm 3.60 \mu\text{m}$ , which did not significantly differ from the results of the previous term of the experiment. However, it was by 30.44 % significantly lower compared to the control values ( $p < 0.05$ ).

The morphometric study of the posterior wall of the eye has found that the ganglion cell layer of the retina measured  $24.89 \pm 2.00 \mu\text{m}$  in the control group of rats.

When consuming monosodium glutamate, sodium nitrite and Ponceau 4R, the average thickness of the ganglion cell layer on week 1 and 4 was  $28.42 \pm 3.30 \mu\text{m}$  and  $27.26 \pm 1.00 \mu\text{m}$ , respectively, which did not significantly differ from the values of the previous period of study, though it was by 9.52 % significantly greater compared to the control group values. On week 8, it measured  $22.00 \pm 1.60 \mu\text{m}$ , which was by 19.30 %

significantly lower compared to the values of the previous period of study but did not significantly differ from the control group results ( $p < 0.05$ ).

On week 12, consumption of food additives led to a decrease in the average thickness of the ganglion cell layer of the rat retina, which measured  $20.97 \pm 1.30 \mu\text{m}$ . These values did not significantly differ from the values of the previous term of the experiment and were by 15.75 % significantly lower compared to the values of the control group ( $p < 0.05$ ).

On week 16 of the observation, the average thickness of the ganglion cell layer of the rat retina did not significantly differ from either the values of the previous term of the experiment or the control group values, amounting to  $21.55 \pm 1.80 \mu\text{m}$  ( $p < 0.05$ ) (Fig. 3).

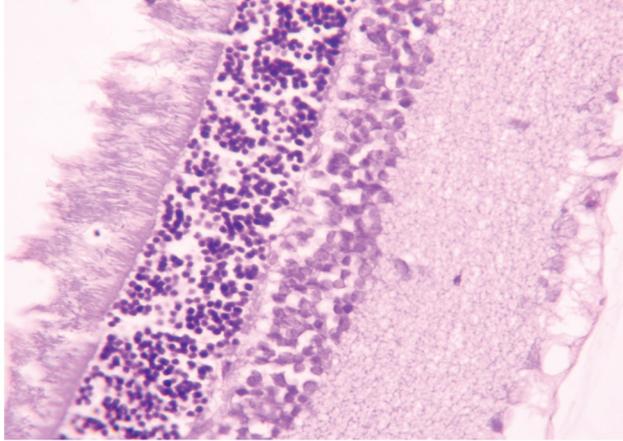


Fig. 3. Destructive changes in the ganglion cell layer of the retina in rats on week 16 of consumption of monosodium glutamate, sodium nitrite and Ponceau 4R. H&E stain. Ocular lens: 10×magnification. Objective lens: 40×magnification.

Thus, the impact of the complex of food additives, namely, monosodium glutamate, sodium nitrite and Ponceau 4R, on the posterior wall of the eye led to a progressive decrease in the morphometric parameters of the average thickness of the posterior wall. At the early stages, this was manifested by a significant reduction by 9.84 % compared to the control group ( $p < 0.05$ ), which was associated with the initial response of the main parameters of the morphological structures of the posterior wall of the eye to the components of the complex of food additives and corresponds to the impact of other exogenous factors on tissues and organs [11, 12]. On week 16 of the experiment, a reduction by 25.27 % in the average values compared to the control group ( $p < 0.05$ ) was noted, indicating a degenerative effect of the chemical compounds in the complex. All major layers of the

retina, including the photoreceptor, outer and inner nuclear layers and ganglion cell layers, exhibited a progressive thinning. However, the ganglion cell layer showed changes throughout the experiment and recovered to the control group values, suggesting compensatory and restorative reactions of the organism. This also supports the idea that sodium nitrite may have a neuroprotective effect, protecting retinal ganglion cells from damage [15]. The average thickness values of the outer and inner nuclear layers were significantly reduced by 30.85 % ( $p < 0.05$ ) and 25.87 %, respectively, without recovery by the end of the study. The thickness of the photoreceptor layer decreased by 25.36 % ( $p < 0.05$ ), indicating a direct effect on the photoreceptors and possible disturbances in the transmission of nerve impulses. One of the components of the food additive complex is monosodium glutamate, which is associated with an increase in calcium levels in retinal cells. This causes oxidative stress, as there is an imbalance between the production of free radicals and the body's ability to neutralize them, which primarily activates a cascade of events leading to apoptosis. This was particularly dangerous for the photoreceptors and ganglion cells of the retina, which are crucial for the visual process. This effect is supported by previously conducted research on the components of the complex [5].

## Conclusion

The impact of the food additive complex of monosodium glutamate, sodium nitrite and Ponceau 4R causes significant morphometric changes in the retinal structures, demonstrating their neurotoxic properties on retinal cells. This is reflected in the progressive reduction of morphometric parameters over time. These changes indicate the development of degenerative alterations, which can affect visual functions, leading to their deterioration. This underscores the need to limit the consumption of food additives to reduce the risks associated with vision impairment.

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### **EFFECT OF THE COMPLEX PROBIOTIC ON LIPID METABOLISM AND OXIDATIVE STRESS AFTER POISONING WITH NICKEL AGAINST THE BACKGROUND OF EXPERIMENTAL ATHEROSCLEROSIS**

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The work studied the effect of the complex probiotic on the state of lipid metabolism and oxidative stress in white male rats after poisoning with nickel nitrate against the background of experimental atherosclerosis. After modeling atherosclerosis, rats were exposed to nickel nitrate for 30 days. In the experimental group, a month after poisoning, the animals received the complex probiotic, which was added to the drinking water of the drinkers for a month. It was found that when male rats were chronically poisoned with nickel nitrate after modeling atherosclerosis, there was a progressive increase in lipid metabolism disorders and oxidative stress processes. The use of a complex probiotic after poisoning with nickel nitrate improved lipid metabolism and oxidative stress. The obtained data show the important practical significance of probiotics in the treatment of nickel poisoning, especially in patients with atherosclerotic vascular damage.

**Key words:** atherosclerosis, lipid metabolism, oxidative stress, nickel, complex probiotic.

### **Р.І. Ібрагімов** **ВПЛИВ КОМПЛЕКСНОГО ПРОБІОТИКА НА ЛІПІДНИЙ ОБМІН І ОКСИДАТИВНИЙ СТРЕС ПІСЛЯ ОТРУЄННЯ НІКЕЛЕМ НА ФОНІ ЕКСПЕРИМЕНТАЛЬНОГО АТЕРОСКЛЕРОЗУ**

У роботі досліджено вплив комплексного пробіотика на стан ліпідного обміну та оксидативний стрес у білих шурів-самців після отруєння нітратом нікелю на фоні експериментального атеросклерозу. Після моделювання атеросклерозу шурів піддавали дії нітрату нікелю протягом 30 днів. У дослідній групі через місяць після отруєння тварини отримували комплексний пробіотик, який протягом місяця додавали до питної води. Встановлено, що при хронічному отруєнні самців шурів нітратом нікелю після моделювання атеросклерозу спостерігається прогресуюче наростання порушень ліпідного обміну та оксидативного стресу. Застосування пробіотика після отруєння нітратом нікелю покращувало ліпідний обмін та оксидативний стрес. Отримані дані свідчать про важливе практичне значення пробіотиків у лікуванні отруєнь важкими металами, особливо у пацієнтів з атеросклеротичним ураженням судин.

**Ключові слова:** шури, атеросклероз, ліпідний обмін, оксидативний стрес, нікель, пробіотик.

The modern environmental situation is characterized by an oversaturation of pollutants of various natures, the most common and dangerous of which are supertoxicants – heavy metals [5]. It has been shown that exposure to heavy metals is an important and underestimated risk factor for the development of atherosclerosis and its consequences [1]. Moreover, heavy metals also damage the intestinal microflora, which plays an important role in the elimination of heavy metals entering through the gastrointestinal tract.