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RESTRUCTURING OF THE RAT PULMONARY VASCULAR BED INDUCED BY THE COMPLEX OF FOOD ADDITIVES

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The paper presents the results of a morphometric study of the vessels' lumen diameter of the large circulatory circle, as well as the vessels of the small circulatory circle of the rats' lungs of under the complex effect of food additives. It was established that the use of a complex of food additives leads to a change in morphometric indicators, and in the early stages it was accompanied by spastic reactions of small circulatory circle pulmonary vessels and vessels of the microcirculatory of the large blood circulation, which was confirmed by a decrease in morphometric indicators of the lumen diameter. During the following periods of study, the vessels of the hemomicrocirculatory channel of the large circulatory circle responded by increasing the average values of morphometric indicators, and of all its links, as a result of the long-term action, first of all, of sodium nitrite on the smooth myocytes of the vessels of the resistive link and the action of compensatory and restorative mechanisms in response to an increase in pulmonary pressure vessels of the small blood circulation to the vessels of the exchange and capacitive links of the large blood circulation. At the end of the experiment, the morphometric indicators did not fully recover, the vessels of the large circulatory circle remained in a decompensated state, which was expressed by an increase in the average values of the morphometric indicators of the diameter of the lumen of the vessels.

Key words: monosodium glutamate, sodium nitrite, Ponceau-4R, blood vessels, lungs, rats.

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СТРУКТУРНА ПЕРЕБУДОВА СУДИННОГО РУСЛА ЛЕГЕНЬ ЩУРІВ ПІД ВПЛИВОМ КОМПЛЕКСУ ХАРЧОВИХ ДОБАВОК

У роботі представлені результати морфометричного дослідження діаметру просвіту судин великого кола кровообігу, так і судин малого кола кровообігу легень щурів при комплексній дії харчових добавок. Встановлено, що вживання комплексу харчових добавок призводить до зміни морфометричних показників та на ранніх стадіях супроводжувалось спастичними реакціями легеневих судин малого та судин мікроциркуляторного русла великого кола кровообігу, що підтверджувалось зменшенням морфометричних показників діаметру просвіту. Протягом наступних термінів дослідження судини гемомікроциркулятоного русла великого кола кровообігу реагували збільшенням середніх значень морфометричних показників, причому всих його ланок, як наслідок тривалої дії перш за все нітриту натрію на гладкі міоцити судин резистивної ланки та дії компенсаторно-відновлювальних механізмів у відповідь на підвищення тиску у легеневих судинах малого кола кровообігу на судини обмінної та ємнісної ланок великого кола кровообігу. На кінець експерименту повного відновлення морфометричних показників не відбувається, судини великого кола кровообігу залишились у декомпенсованому стані, що виражалось збільшенням середніх значень морфометричних показників діаметру просвіту судин.

Ключові слова: глутамат натрію, нітрит натрію, Понсо- 4R, судини, легені, щури.

The study is a fragment of the research project "Restructuring of the organs of the immune, respiratory and excretory systems under the effect of various exogenous factors (monosodium glutamate, sodium nitrite, ethanol, methacrylate)", state registration No. 0121U108234.

The use of food additives causes significant controversial opinions both in the scientific community and in the public, mainly due to the lack of thorough research on their impact on the human body, especially under their combined action. The conducted investigations 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 effect have been found to date [3].

The analysis of the content of food additives showed that monosodium glutamate, sodium nitrite and Ponceau-4 are most widely used in foreign and domestic food products.

Monosodium glutamate, as an additive, is now indispensable in the food production. At the same time, the safety of E621 and the effect of this substance require further research. A critical analysis of the existing literature shows that many of the negative reports of the health consequences of monosodium glutamate are uninformative, as they are based on excessive dosage that does not correspond to the norms commonly used in food products [7, 15].

Food additive E-250 (sodium nitrite) is widely used as a color retainer and food preservative in the manufacture of various types of meat products. Sodium nitrite has the ability to attach to blood cells and interfere with oxygen transport, has a harmful toxic effect on various organs of the body [8]; consumption

of sodium nitrite significantly increased markers of renal dysfunction, oxidative stress, inflammation and apoptosis [5].

Ponceau-4R food colorant is widely used in the food industry, giving the products a required color from yellow to maroon [13].

Colorants, entering the body as haptens, binding to proteins such as serum albumin and others, become full-fledged antigens to which antibodies are synthesized. Permissible sanitary and hygienic standards are usually exceeded, which increases their allergenicity [4].

It is known that two main systems are involved in the functioning of the lungs: the airways and blood vessels, which are structurally connected by the interstitial stroma, which runs throughout the lung and join its various parts [1].

Pulmonary circulation has a system that provides gas exchange (vessels of the small circle of blood circulation), and a system that supplies blood to the tissues of the airways and vessels of the small circle (vessels of the large circle of blood circulation). Generally, in terms of ensuring breathing, hemodynamics can be considered first of all, starting with the vessels of the small circle; however, its value was assessed only after the blood circulation is studied as a whole.

The purpose of the study was to establish the dynamics of changes in the metric parameters of the lumen diameter of the microcirculatory vessels of the large circle of blood circulation and pulmonary vessels of the small circle of blood circulation under normal conditions and under the complex action of food additives: monosodium glutamate, sodium nitrite and Ponceau-4R.

Material and Methods. 84 mature outbred male rats were involved into the study. The rats of control group (n=10) consumed drinking water and were administered with saline orally. The rats of the experimental group, with access to water *ad libitum*, were administered with 0,6 mg/kg sodium nitrite, 20 mg/kg monosodium glutamate and 5 mg/kg Ponceau 4R in 0.5 ml of distilled water once daily per os. Notably, the doses of food additives were twice lower the allowable normal rate in food products. The "open field" test was used to evaluate the rats' adaptive behavior [12]. The animals were sacrificed within 1, 4, 8, 12 and 16 weeks under thiopentone anesthesia overdose. After animals' euthanasia, the fragments of the lungs were fixed in 10 % formalin solution. Subsequently, the pieces of the lungs were embedded into paraffin, using the conventional technique [9]. Sections of 5-10 μm thick were obtained using the ARM 3600 microtome. After staining with hematoxylin and eosin, the sections were placed in polystyrene and studied under the light microscope. The digital microscope, equipped with the Levenhuk D740T digital microphoto attachment, and adapted software have been used for microphotography and morphometric study. Statistical processing of morphometric data was performed using the Excel program [2]. The housing of the animals and experimental part of the study has been carried out in compliance with the "General ethical principles used for animal experiments", adopted at the I National Congress on Bioethics and requirements of the international principles of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" [6].

Results of the study and their discussion. A morphometric study of the diameter of the lumen of the blood vessels of the microcirculatory bed of the large circle of blood circulation of the rat lungs showed that in the control group of animals, the diameter of the lumen of arterioles, capillaries and venules was 24.76±0.29 μm, 4.11±0.17 μm, and 49.43±0.27 μm, respectively (Table 1).

Table 1

Morphometric characteristics of the elements of the microcirculatory bed of the large circle of blood circulation of the rat lungs

Parameters	Vessels of the microcirculatory bed		
	diameter of the lumen of arterioles	diameter of the lumen of capillaries	diameter of the lumen of venules
Control group	24.76±0.29	4.11±0.17	49.43±0.27
Week 1	22.89±0.17 *	3.34±0.11 *	49.42±0.30
Week 4	13.87±0.08 *.**	5.53±0.13 *.**	39.82±0.15 *.**
Week 8	24.05±0.26 *.**	5.98±0.11 *.**	42.64±0.19 *.**
Week 12	26.17±0.12 *.**	6.26±0.16 *.**	42.07±0.13 *.**
Week 16	25.33±0.36 *.**	7.20±0.08 *.**	50.51±0.61 *.**

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

Collagen fibers and fibroblasts were detected in the interstitial pulmonary connective tissue. The wall of arterioles was constructed of three layers and consisted of an inner layer of elongated endotheliocytes located on the basal membrane; an inner elastic membrane demarcated the middle layer of smooth muscle cells. Adventitial cells were located outside (fig. 1).

Consumption of the complex of food additives after 1 week of the experiment led to a decrease in the average values of the lumen diameter of arterioles and capillaries by 7.55 % (22.89±0.17 μm) and 18.73 % (3.34±0.11 μm), respectively; however, the diameter of the lumen of venules did not significantly differ from the average values in control group of rats, accounting for 49.42±0.30 μm ($p<0.05$).

After 4 weeks of consumption of monosodium glutamate, sodium nitrite and Ponceau 4R in the experiment, the resistance section responded with significant decrease in the average values of the diameter of the lumen by 39.41 % ($p<0.05$), compared to the previous period, which were 13.87±0.08 μm that was also by 43.98 % significantly lower than the value in the control group of animals ($p<0.05$). The vessels of the exchange section responded with a significant lumen dilatation by 65.57 %, compared to the values of week 1 of the experiment, which was also by 34.55 % greater than the values of the control group ($p<0.05$). The average values of the diameter of the lumen of the capillaries on week 4 were 5.53±0.13 μm. The capacitance section showed a decrease in the average values to 39.82±0.15 μm, which was significantly by 19.43 % lower than the values of the previous time period of the experiment, and by 19.44 % lower than its value in the control group ($p<0.05$).

The lumen of the arterioles was nonuniform, the internal elastic membrane was tortuous, smooth myocytes with clear cytoplasm were detected in the middle membrane. Edema and leukocyte infiltration from the alveolar surface were observed perivascularly, capillaries from the adjacent lymphoid tissue were dilated; no formed elements of blood were noted in the lumen, and endotheliocytes were flattened (fig. 2).

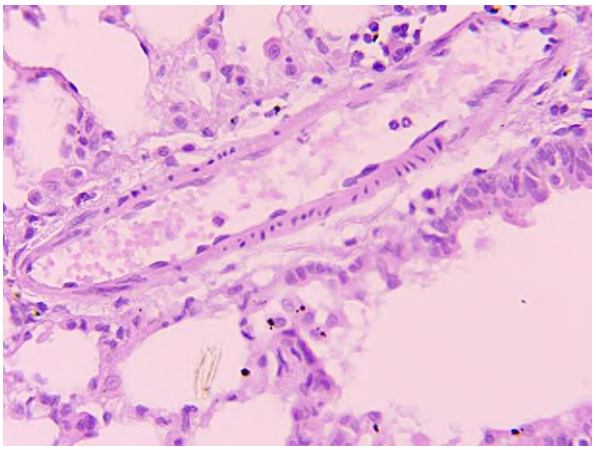

Fig. 1. Arteriole in the interstitial tissue of the lungs of rats of the control group. H&E stain. Oc. lens: 10×magnification; ob. lens: 40× magnification.

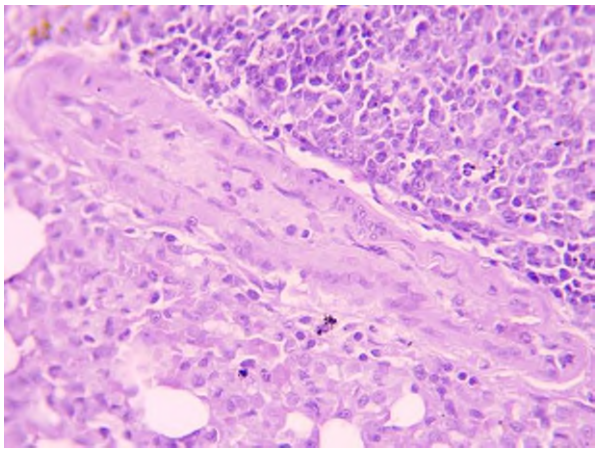

Fig. 2. Spasm of the arteriole of the large circle of blood circulation of rats' lungs on week 4 of consumption of the complex of food additives. H&E stain. Oc. lens: 10×magnification; ob. lens: 40× magnification.

On week 8, consumption of the complex of food additives led to a significant increase in the average values of the diameter of the lumen of arterioles by 73.40 %, compared to the results obtained on week 4, which was by 2.87 % significantly lower than the values of the control group ($p<0.05$). The value of the diameter of the lumen of arterioles on week 8 was 24.05±0.26 μm ($p<0.05$). The morphometric parameters of the diameter of the capillary lumen increased significantly, both compared to the previous period of the study (by 8.14 % ($p<0.05$)), and to the control group (by 45.50 % ($p<0.05$)), accounting for 5.98±0.11 μm. On week 8, the venules responded by dilatation of the lumen, which was confirmed by a significant increase in its mean values by 7.08 % ($p<0.05$), compared to the previous period of the study; however, the above parameters were by 13.74 % significantly lower than the values in the control group of animals (42.64±0.19 μm ($p<0.05$)).

On week 12 of the consumption of the complex of monosodium glutamate, sodium nitrite and Ponceau 4R, the morphometric parameters of the diameter of the lumen of arterioles were 26.17±0.12 μm, which was by 8.81 % significantly higher than the value of the previous period of the experiment, and by 5.69 % higher than the values in the control group ($p<0.05$). The mean values of the diameter of the lumen of the capillaries significantly increased to 6.26±0.16 μm. The parameters were by 4.68 % higher compared to the values on week 8 of the experiment which was by 52.31 % significantly higher compared to the parameters of the control group of rats ($p<0.05$) The diameter of the lumen of the venules was significantly reduced by 1.34 %, when compared with its value on week 8, which was also by 14.89 % significantly lower than the value of the control group of animals ($p<0.05$). The average values of the diameter of the lumen of the venules on week 12 were 42.07±0.13 μm ($p<0.05$).

At the end of the experiment, the impact of the complex of food additives led to a decrease in the diameter of the lumen of the arterioles of the large circle of blood circulation of the lungs by 3.21 % ($p<0.05$), accounting for 25.33±0.36 μm, but its mean values were by 2.30 % significantly greater than the parameters of

the control group (p <0.05). The values of the lumen of the vessels of the exchange section were by 15.02 % significantly greater compared to the previous period of the experiment which was by 75.18 % significantly higher than the parameters of the control group of rats (p<0.05). The diameter of the capillary lumen was 7.20±0.08 μm. The vessels of the capacitance section showed a steady increase in the diameter of the lumen with the mean values of 50.51±0.61 μm, which was significantly greater compared both to the parameters of the week 12 of the experiment (by 20.06 %) and their mean values in the control group of animals (by 2.18 %) (p<0.05).

The morphometric study of the vessels of the small blood circulation of the rats' lungs has established that in rats of the control group, the diameter of the lumen of the arteries was 235.20±1.29 μm, and the mean values of the diameter of the lumen of the veins eeee 299.12±0.51 μm (Table 2).

Table 2

Morphometric characteristics of the vessels of the small circle of blood circulation of the rats' lungs

Parameters	Vessels of the small circle of blood circulation	
	Diameter of the lumen of arteries	Diameter of the lumen of veins
Control group	235.20±1.29	299.12±0.51
Week 1	131.92±0.41 *	243.65±0.53 *
Week 4	210.11±0.81 *.**	262.44±0.33 *.**
Week 8	213.60±1.26 *.**	255.82±1.09 *.**
Week 12	184.35±0.30 .**	244.91±0.51 *.**
Week 16	212.84±0.88 *.**	262.88±1.06 *.**

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

On week 1 of the experiment, a significant decrease in the average values of the diameter of the lumen of the arteries by 43.91 % (131.92±0.41 μm), and a significant decrease in the average values of the diameter of the lumen of the veins of the small circle of the blood circulation by 18.54 % (243.65±0.53 μm) (p <0.05) was noted.

Under the influence of the complex of food additives, the diameter of the lumen of the arteries of the small circle of blood circulation on week 4 of the experiment was 210.11±0.81 μm, which was by 59.27 % significantly greater than the values of the week 1 of the experiment, though it was by 10.67 % lower than the results in the control group of rats (p<0.05). The average values of the veins also increased significantly by 7.71 % compared to the previous period of the experiment, accounting for 262.44±0.33 μm, and at the same time, it was also by 12.26 % significantly lower than the parameters of the control group (p<0.05).

The mean values of the diameter of the lumen of the arteries on week 8 of the consumption of monosodium glutamate, sodium nitrite and Ponceau 4R were 213.60±1.26 μm that was by 1.66 % significantly greater than the values of week 4 of the experiment; however, it was by 9.18 % significantly lower than the values of the control group (p<0.05). The diameter of the lumen of the veins also significantly decreased compared to the results of the previous time period of the experiment by 2.52 %, accounting for 255.82±1.09 μm, which was by 15.48 % significantly lower than the values of the control group (p<0.05).

On week 12 of the effect of the complex of food additives, a significant decrease in the mean values of the diameter of the lumen of the arteries was noted, accounting for 184.35±0.30 μm, which was by 13.69 % lower than the values on week 8 of the experiment and by 21.62 % lower than the results of the control groups of animals (p<0.05). The veins responded by narrowing of the lumen, with average values of 244.91±0.51 μm, which, respectively, were by 4.26 % significantly lower than the values of the previous time period of the experiment and by 18.12 % significantly lower than the values in the control group of rats (p<0.05).

Consumption of the complex of monosodium glutamate, sodium nitrite and Ponceau 4R on week 16 of the experiment led to an increase in the mean diameter of the lumen of the arteries of the small circle of blood circulation of the rats' lungs, accounting for 212.84±0.88 μm, and were by 15.45 % significantly greater than the values of the previous period of the experiment; however, they were by 9.51 % significantly lower than the parameters in the control group (p<0.05). The diameter of the lumen of the veins also increased by 7.34 % compared to the results on the week 12, and was by 12.12 % significantly lower than the values in the control group of rats (p<0.05); the mean values of the diameter of the lumen of the veins on week 16 were 262.88± 1.06 μm.

An increase in the tone of arterial vessels was accompanied by the phenomenon of folding and corrugation of the internal elastic membrane, the muscular membrane was thickened with a simultaneous

narrowing of the lumen. Edema developed in the structural elements of the vascular walls. Cytoplasm of smooth muscle cells was clear; swelling of the nuclei of the endothelium and their protrusion into the lumen of the arteries was noted, and their adluminar contour was tortuous (fig. 3).

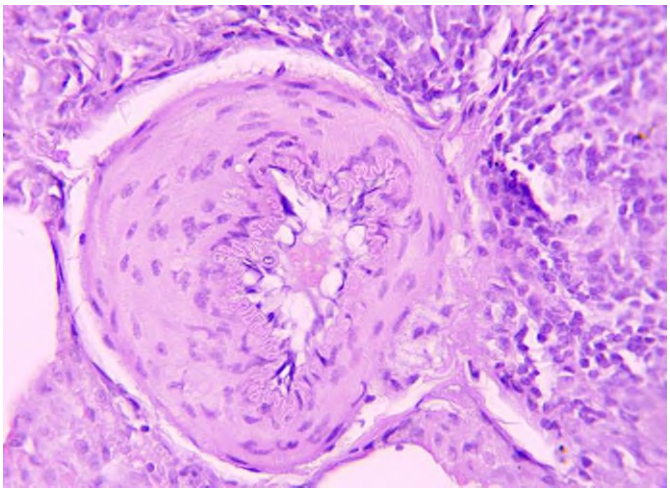

Fig. 3. Thickening of the walls of the arteries of the vessels of the small circle of blood circulation of rats' lungs rats on week 16 of consumption of the complex of monosodium glutamate, sodium nitrite and Ponceau 4R. H&E stain. Oc. lens: 10×magnification; ob. lens: 40× magnification.

Thus, it should be noted that the changes occurred simultaneously both in the vessels belonging to the large circle of blood circulation and in the vessels of the small circle of blood circulation, that is, the structural response of the vessels had a non-specific character. The course at the early stages of the consumption of the complex of food additives of monosodium glutamate, sodium nitrite and Ponceau 4R was accompanied by spastic reactions of pulmonary vessels of the small circle of blood circulation and vessels of the microcirculatory bed of the large circle of blood circulation, which was confirmed by a decrease in the morphometric values of the diameter of the lumen due to the action of the chemical components of the food additive complex. The available parameters were identified with the data from previously conducted studies regarding the primary impact of exogenous factors on the tissues and vessels of internal organs, which led to the occurrence of hypoxia [9, 10]. As a result, the activation of tissue mast cells led to an increase in the permeability of the vessel walls, followed by the formation of edema in the interstitium and paravasal spaces of the vessels of a microcirculatory bed of the large circle of blood circulation and increased pressure in the pulmonary vessels of the small circle of blood circulation. During the following periods of study, the vessels of the microcirculatory bed of the large circle of blood circulation responded by increasing the average values of morphometric parameters, and of all its sections, as a result of the long-term impact, first of all, of sodium nitrite on the smooth myocytes of the vessels of the resistance section [11], which led to a decrease in pressure and resulted in dilatation of the lumen of the vessels of the exchange and capacitance sections; secondly, a decrease in the average morphometric parameters of the diameter of the lumen of the pulmonary vessels led, on the contrary, to an increase in the pressure in the vessels of the small circle of blood circulation, which causes a decrease in the intensity of gas exchange processes, resulting in the decrease in blood oxygenation; however, due to the presence of arterio-venular anastomoses in the middle of the experiment, a partial recovery of the parameters was noted, which was expressed by an increase in the mean values of the results of the morphometric study of the diameter of the lumen of the vessels of the small circle of blood circulation, and at the end of the experiment, the values remained permanently low, showing a decrease in the diameter of the lumen of arteries by 9.51 % compared to the parameters in the control group ($p<0.05$), and the lumen of veins by 12.12 % ($p<0.05$). Disruption of oxygenation processes caused the development of dystrophic processes and violation of normal tissue-vascular relationships of the vessels of the large circle of blood circulation. During the experiment, compensatory and adaptive reactions occurred in parallel with the development of signs of destruction in the middle of the experiment, where an increase in the secretory activity of goblet cells, dilatation of the lumen of individual alveoli, thickening of interalveolar septa, swelling of the structural elements of the vascular walls was observed [14]. At the end of the experiment, the morphometric parameters did not fully restore, the vessels of the large circle of blood circulation remained in a decompensated state, which was expressed by the dilatation of the lumen and, accordingly, an increase in the mean values of the morphometric parameters of the diameter of the lumen of the vessels.

Conclusion

Consumption of the complex of food additives leads to changes in morphometric parameters simultaneously both in the vessels of the large and small circles of blood circulation. The course of the early stages of consumption of the complex of monosodium glutamate, sodium nitrite and Ponceau-4R was accompanied by spastic reactions of small pulmonary vessels and vessels of the microcirculatory bed of the large circle of blood circulation, which was confirmed by a decrease in the morphometric parameters of the diameter of the lumen. During the following periods of study, the vessels of the microcirculatory bed

of the large circle of blood circulation responded by increasing the average values of morphometric parameters, and of all its sections, as a result of the long-term impact, first of all, of sodium nitrite on the smooth myocytes of the vessels of the resistance section and the action of compensatory and restorative mechanisms in response to an increase in pulmonary pressure in the vessels of the small blood circulation, which leads to a decrease in the degree of oxygenation, on the vessels of the exchange and capacitance sections of the large circle of blood circulation. At the end of the experiment, the morphometric parameters did not fully restore, the vessels of the large circle of blood circulation remained in a decompensated state, which was expressed by an increase in the average values of the morphometric parameters of the diameter of the lumen of the vessels.

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