

G. A. Yeroshenko, A. S. Grygorenko, K. V. Shevchenko, O. D. Lysachenko,
V. N. Sokolenko, T. V. Khilinska, V. P. Bilash, A. V. Solod
Poltava State Medical University, Poltava
Poltava V.G. Korolenko National Pedagogical University, Poltava

REACTIVE CHANGES IN THE VESSELS OF THE RAT'S DUODENAL MUCOSA IN RESPONSE TO THE EFFECT OF COMPLEX FOOD ADDITIVES

e-mail: gala_umsa@ukr.net

The paper presents the findings of the morphometric study on the complex action of food additives on the state of the vessels of the mucous membrane. It has been found that at the early stages of observation, the effect of monosodium glutamate, sodium nitrite and Ponceau 4R led to the lowering of the mean values of the metric parameters of the vessels of the blood microcirculatory bed of the mucous membrane and dilatation of the lumen of larger vessels of the submucous layer. Further development of the inflammatory reaction with edema led to a decrease in the diameters of the lumen of the vessels of the resistance and exchange sections with dilatation of the lumen of the venules, caused hypoxia and dystrophic lesions, followed by restoration of the values, due to compensatory-adaptive responses to irritating factor, though no complete normalization occurred. Changes in the vessels of the submucous layer depended on the state of the vessels of the mucous membrane throughout the experiment.

Keywords: duodenum, vessels, food additives, mucous membrane, rats.

Г.А. Єрошенко, А.С. Григоренко, К.В. Шевченко, О.Д. Лисаченко, В.Н. Соколенко,
Т.В. Хілінська, В.П. Білаш, А.В. Солод

РЕАКТИВНІ ЗМІНИ СУДИН СЛИЗОВОЇ ОБОЛОНКИ ДВАНДЦЯТИПАЛОЇ КИШКИ ЩУРІВ НА ВПЛИВ КОМПЛЕКСУ ХАРЧОВИХ ДОБАВОК

В роботі представлені дані морфометричного дослідження при комплексній дії харчових добавок на стан судин слизової оболонки. Встановлено, що дія глутамату натрію, нітриту натрію та Понсо 4R на ранніх термінах спостереження визначається зменшення середніх значень метричних показників судин гемомікроциркуляторного русла слизової оболонки, та розширення просвіту судин крупного калібру підслизової основи. В подальшому розвиток запальної реакції з виникненням набряку призвів до зменшення діаметрів просвіту резистивної та обмінної ланок з розширенням просвіту венул, викликав виникнення гіпоксії та дистрофічних змін, з наступним відновленням показників, внаслідок компенсаторно- пристосувальних реакцій на дію подразнюючого фактору, але повної нормалізації не відбулося. Зміни судин підслизового прошарку залежали від стану судин слизової оболонки протягом експерименту.

Ключові слова: дванадцятипала кишка, судини, харчові добавки, слизова оболонка, щури.

The paper 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 state of the sections of the microcirculatory bed has a significant impact on the body organs, which is crucial for their normal functioning [14].

It is known that the duodenum has a common blood, lymphatic and innervation relationship with the adjacent organs. Consequently, pathological processes occurring in these organs, could cause changes in the microcirculatory bed of the duodenum, altering its functional state [4].

Current scientific publications elucidate the results of the effects of various food additives on the organs and systems; however, insufficient data have been found to date [1–3].

The most common and widespread flavor enhancer is monosodium glutamate (E-621), which enhances taste sensations by increasing the sensitivity of the taste buds of the tongue [6]. Many foreign researchers report on their concern over the potential impact on the human health, pathophysiological and toxicological effects of monosodium glutamate [10], emphasizing its harmful effect. The findings of the studies have shown that prolonged daily consumption of monosodium glutamate, even in safe doses, leads to morphological changes in the colon wall in the form of focal inflammatory changes of the mucous membrane, circulatory disorders in the wall, erosive ulcers, as well as dysplastic alterations that could be dangerous in terms of potentiation of carcinogenesis in the colon mucosa [5].

In Ukraine, the food additive E250 (sodium nitrite) is widely used as a color retainer in manufacturing meat products [9]. Experimental study of the state of the hemo- and lympho-microcirculatory bed of the mesentery of the rats' small intestine in the dynamics of acute oral poisoning with sodium nitrite has found the phenomena of vasodilation of the resistance section with a decrease in the rhythm of their vasomotion, venular hypertension, increased venous-arterial shunting, vascular tortuosity, stasis of erythrocyte aggregation with paravasal tissue edema [8].

Food colorants are very popular in the food industry, giving the product an attractive appearance, and one of them is E124 food additive [12]; however, most of synthetic colorants are harmful for human health. That is due to the product of their cleavage, benzidine, which induces various tumors in humans and animals. Another component of the azo dye, p-phenylenediamine, is a contact allergen. [11].

The purpose of the study was to establish the dynamics of changes in the metric parameters of the blood microcirculatory bed of the mucous membrane and the vessels of the submucous layer of the rat duodenum in normal condition and under the effect of monosodium glutamate, sodium nitrite and Ponceau 4R complex food additives.

Material and methods. 84 outbred mature male rats were involved into the experiment. The rats of control group consumed drinking water and received saline per os. The rats of the experimental group, with access to water ad libitum, consumed 10 % sodium nitrite solution. Monosodium glutamate was administered at a dose of 20 mg/kg in 0.5 ml of distilled water, Ponceau 4R at a dose of 5 mg/kg in 0.5 ml of distilled water once daily per os. The doses of food additives were twice lower the allowable normal rate in food products. The evaluation of the rats' adaptive behavior was made with the use of the "open field" test. [15].

The animals were sacrificed within 1, 4, 8 and 16 weeks under thiopentone anesthesia overdose. After euthanasia, the fragments of the duodenal wall were fixed in 10% neutral formalin solution for three days. Subsequently, the pieces of the duodenal wall, fixed in formalin, were embedded into paraffin [13]. Sections of the 5–10 μm thick were obtained using the sliding microtome and were mounted on the slides by stenciling technique. After staining with hematoxylin and eosin, the sections were enclosed into polystyrene and studied in the light microscope. The light microscope equipped with DCM 900 digital microphoto attachment and software, adapted to the studies, have been used for microimaging and morphometric study. Statistical processing of morphometric data was made using the Excel software [7].

Results of the study and their discussion. Morphometric study of the diameter of the lumen of the vessels of the blood microcirculatory bed of the rat duodenal mucosa showed that in control rats, the diameter of the lumen of arterioles, capillaries and venules was $12.51 \pm 0.01 \mu\text{m}$, $4.23 \pm 0.04 \mu\text{m}$ and $16.5 \pm 0.05 \mu\text{m}$, respectively (table 1).

Table 1

Morphometric characteristics of the elements of the blood microcirculatory bed of the rat duodenal mucosa

| Parameters | Mucous membrane (μm) | | |
|------------|-----------------------------------|----------------------|-----------------------|
| | Arterioles | Capillaries | Venules |
| Control | 12.51 ± 0.01 | 4.23 ± 0.04 | 16.58 ± 0.05 |
| Week 1 | $12.30 \pm 0.02^*$ | $3.93 \pm 0.03^*$ | $15.78 \pm 0.04^*$ |
| Week 4 | $12.84 \pm 0.03^{**}$ | $4.91 \pm 0.03^{**}$ | $15.94 \pm 0.03^{**}$ |
| Week 8 | $12.36 \pm 0.03^{**}$ | $3.58 \pm 0.02^{**}$ | $19.13 \pm 0.03^{**}$ |
| Week 12 | $13.02 \pm 0.02^{**}$ | $3.78 \pm 0.03^{**}$ | $16.99 \pm 0.03^{**}$ |
| Week 16 | $13.34 \pm 0.03^{**}$ | $4.00 \pm 0.02^{**}$ | $19.72 \pm 0.03^{**}$ |

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, consumption of complex food additives led to a decrease in the mean values of the diameter of the lumen of the arterioles by 1.68 % ($p < 0.05$), constituting $12.30 \pm 0.02 \mu\text{m}$; capillaries by 7.09 % ($p < 0.05$), constituting $3.93 \pm 0.03 \mu\text{m}$; venules by 4.83 % ($p < 0.05$) with its mean values of $15.78 \pm 0.04 \mu\text{m}$ (table 1).

On week 4 of the experiment, the resistance section responded with a significant increase in the mean values of the lumen diameter by 4.49 % ($p < 0.05$), compared to the previous period, constituting $12.84 \pm 0.03 \mu\text{m}$, which was also significantly greater the value of the control group of animals by 2.64 % ($p < 0.05$). The vessels of the exchange section also responded with a significant dilatation of the lumen by 24.94 %, compared to the results on week 1 of the experiment, which was also by 16.08 % greater the values of the control group ($p < 0.05$). The mean values of the diameter of the lumen of the capillaries on week 4 were $4.91 \pm 0.03 \mu\text{m}$. The capacitance section responded with increase in the mean values $15.94 \pm 0.03 \mu\text{m}$, which was significantly by 1.01% greater than the values of the previous period of the experiment, and by 3.86 % greater than its value in the control group ($p < 0.05$) (Table 1).

Visual examination of the vessels in the duodenal wall has found significant changes in the typical elements of the wall. The phenomena of the edema was observed in the mucous membrane, which led to

an increase in the amount of amorphous substance, as a result of which the venule wall was deformed, a small number of blood corpuscles were observed in the vascular lumen, the tunica adventitia consisted of loose fibrous connective tissue and was thickened (fig. 1).

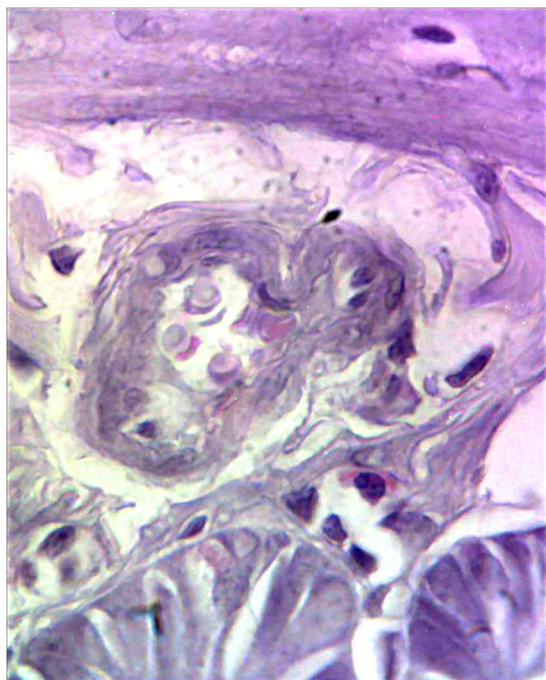


Fig. 1. Edema of the rat duodenal mucosa on week 4 of consumption of complex food additives. H&E stain. Ocular lens: 10× magnification, objective lens: 100× magnification.

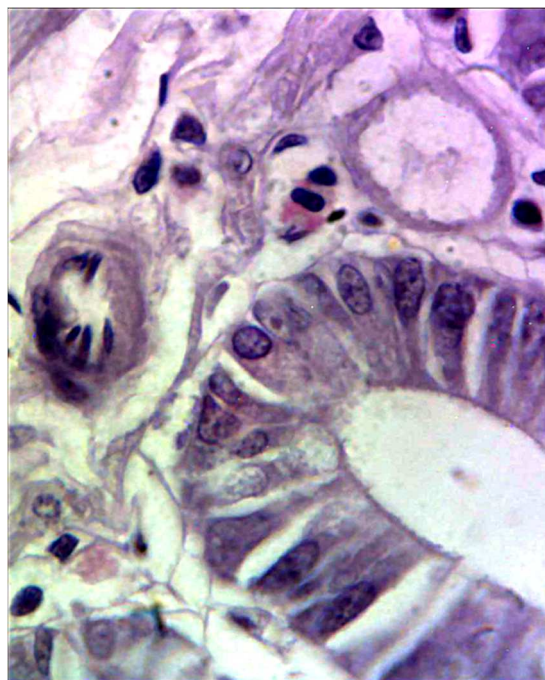


Fig. 2. Vessels of the blood microcirculatory bed of the rat duodenal mucosa on week 8 of consumption of complex food additives. H&E stain. Ocular lens: 10× magnification, objective lens: 100× magnification.

The combined effect of monosodium glutamate, sodium nitrite and Ponceau 4R on week 8 led to a decrease in the mean values of the diameter of the lumen of the arterioles by 3.74 %, compared to the results obtained on week 4, which was also by 1.2 % ($p < 0.05$) significantly lower compared to the control group. The values of the diameter of the lumen of the arterioles on week 8 were $12.36 \pm 0.03 \mu\text{m}$. Morphometric parameters of the capillary lumen diameter significantly decreased by 27.09 % ($p < 0.05$) and 15.37 % ($p < 0.05$) compared to the previous study period and the control group, respectively, accounting for $3.58 \pm 0.02 \mu\text{m}$. On week 8, the venules responded with a persistent dilatation of the vascular lumen, which was confirmed by a significant increase in mean values to $19.13 \pm 0.03 \mu\text{m}$. These values were greater compared to the values of the previous period of the experiment by 20.01 %, and by 15.38 % greater compared to the control group of animals ($p < 0.05$) (table 1).

Histological examination of the elements of the blood microcirculatory bed revealed changes in the structural components in the wall of arterioles, in which under the influence of complex food additives the tunica intima was formed by a layer of endothelial cells, the nuclei of which protruded in the lumen. Disrupted contacts between smooth myocytes were noted in the tunica media. The capillaries were in spasm and barely detected on the specimens. The visual analysis of the vessels of the capacitance section revealed a significant dilatation of the lumen of the vessels with thinning of the tunica adventitia, in the venules of the mucous membrane the phenomena of desolation were noted (fig. 2).

On week 12 of complex food additives consumption the morphometric values of the diameter of the lumen of the arterioles were $13.02 \pm 0.02 \mu\text{m}$, which was by 5.34 % significantly greater than the value of the previous period of the experiment, and by 4.08 % greater than the values of the control group ($p < 0.05$). The mean values of the diameter of the lumen of the capillaries significantly increased to $3.78 \pm 0.03 \mu\text{m}$. These values were by 5.59 % greater than their values on week 8 of the experiment, though significantly lower than the values of the control group by 10.64 % ($p < 0.05$). The diameter of the lumen of the venules significantly decreased by 11.19 %, compared to its value on week 8, though was by 2.47 % larger than the value of the control group ($p < 0.05$). The mean values of diameter of the lumen of the venules on week 12 were $16.99 \pm 0.03 \mu\text{m}$ (table 1).

The effect of the complex food additives on week 16 led to increase of the diameter of the lumen of the arterioles of the rat duodenal mucosa by 2.46 % ($p < 0.05$), accounting for $13.34 \pm 0.03 \mu\text{m}$. Its mean values were also significantly greater than the values of the control group by 6.63 % ($p < 0.05$). The values

of the lumen of the vessels of the exchange section significantly increased compared to the previous period of the experiment by 5.82 %, but remained significantly lower than the values of the control group of rats by 5.44 % ($p < 0.05$). The diameter of the lumen of the capillaries was $4.00 \pm 0.02 \mu\text{m}$. The vessels of the capacitance section showed persistent increase in the diameter of the lumen, with mean values of $19.72 \pm 0.03 \mu\text{m}$, which were by 16.07 % and 18.94 % significantly greater than the values on week 12 of the experiment and their mean values in the control group of animals, respectively ($p < 0.05$) (table 1).

The nuclei of the vast majority of endothelial cells of the inner layer of the venules were flattened, indicating the stretching of blood microvessels, with the phenomena of desolation; blood plasma had a heterogeneous optical density. Areas of thinning of the vascular wall of the capacitance section of the blood microcirculatory bed were visualized (fig. 3).

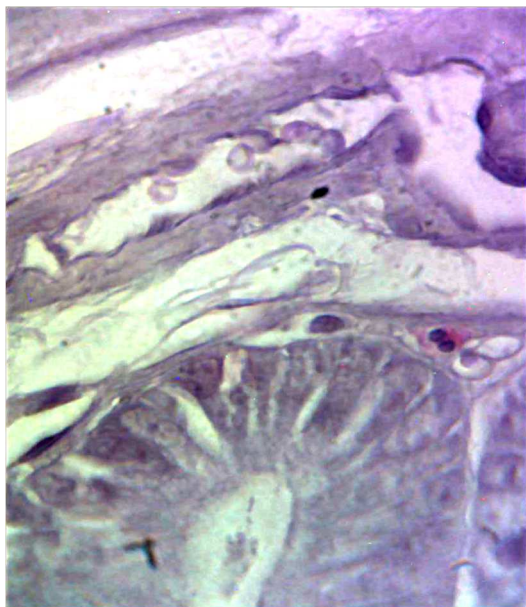


Fig. 3. Vessels of the blood microcirculatory bed of the rat duodenal mucosa on week 16 of the experiment. H&E stain. Ocular lens: $10\times$ magnification, objective lens: $100\times$ magnification.

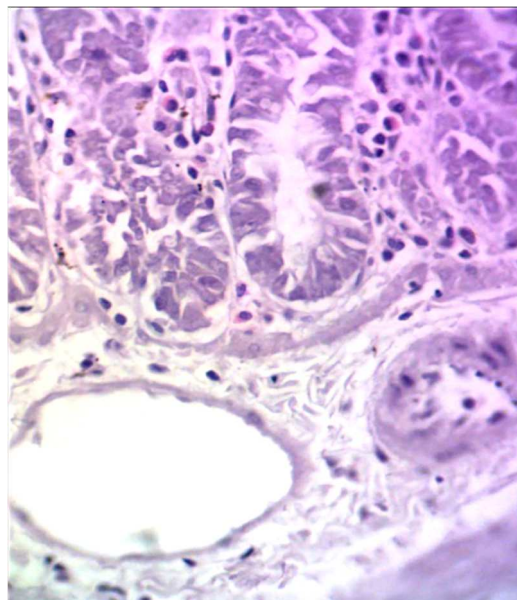


Fig. 4. Dilatation of the venules and arterioles of the submucous layer of rat duodenum on week 8 of consumption of complex food additives. H&E stain. Ocular lens: $10\times$ magnification, objective lens: $40\times$ magnification.

Table 2

Morphometric characteristics of vessels of submucous layer of rat duodenum

| Parameters | Submucous layer (μm) | |
|------------|-----------------------------------|-------------------------|
| | Arteries | Veins |
| Control | 18.56 ± 0.02 | 28.48 ± 0.02 |
| Week 1 | $24.13 \pm 0.03^*$ | $43.90 \pm 0.03^*$ |
| Week 4 | $23.12 \pm 0.04^{*,**}$ | $35.17 \pm 0.12^{*,**}$ |
| Week 8 | $22.02 \pm 0.05^{*,**}$ | $31.56 \pm 0.04^{*,**}$ |
| Week 12 | $25.73 \pm 0.04^{*,**}$ | $35.35 \pm 0.05^{*,**}$ |
| Week 16 | $18.15 \pm 0.02^{*,**}$ | $45.09 \pm 0.07^{*,**}$ |

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

Morphometric study of larger vessels of the submucous layer has found that the mean values of the diameter of the lumen of the arteries was $18.56 \pm 0.02 \mu\text{m}$, the diameter of the lumen of the veins was $28.48 \pm 0.02 \mu\text{m}$ (table 2).

The findings showed that on week 1 of the experiment a significant increase in the mean values of the arteries and veins by 30.01 % ($24.13 \pm 0.03 \mu\text{m}$) ($p < 0.05$) and 54.14 % ($43.90 \pm 0.03 \mu\text{m}$) ($p < 0.05$), respectively, was noted (table 2).

Under the effect of complex food additives, the diameter of the lumen of the arteries of the submucous layer of the duodenum on week 4 of the experiment was $23.12 \pm 0.04 \mu\text{m}$ that was by 4.19 % significantly lower the values on week 1 of the experiment, though by 24.57 % significantly greater than the results of the control group of rats ($p < 0.05$). The mean values of veins significantly decreased by 19.89 % compared to the previous period ($p < 0.05$), accounting for $35.17 \pm 0.12 \mu\text{m}$, though it was by 23.49 % ($p < 0.05$) significantly greater than the value of the control group (table 2).

The mean values of the diameter of the lumen of the arteries on week 8 accounted for $22.02 \pm 0.05 \mu\text{m}$ and were by 4.76 % lower the value on week 4 of the experiment, though it was by 18.74 % ($p < 0.05$) significantly greater than the values of the control group. The diameter of the venous lumen also decreased significantly compared to previous results by 10.26 % ($p < 0.05$), accounting for $31.56 \pm 0.04 \mu\text{m}$, which was by 10.81% ($p < 0.05$) significantly greater than the values of the control group (table 2).

Histological study revealed reduced swelling, which was confirmed by a decrease in the amount of amorphous substance; collagen fibers were stratified by amorphous substance of low optical density and were packed evenly. In the submucous layer, dilatation of veins and arteries was visualized. The wall of the veins was thinned; no blood corpuscles were found in the lumen. In the lumen of the arteries, sporadic erythrocytes and endotheliocytes were flat (fig. 4).

The effect of the complex food additives on week 12 showed significant increase in the mean values of the diameter of the lumen of the arteries, accounting for $25.73 \pm 0.04 \mu\text{m}$, which was by 16.84 % greater the value on week 8 of the experiment and by 38.63 % greater than the results of the control group ($p < 0.05$). The veins responded by dilating the lumen, with mean values of $35.35 \pm 0.05 \mu\text{m}$, which, respectively, were by 12.01 % greater than the values of the previous period of the experiment and by 24.12 % significantly greater the values of the control group ($p < 0.05$) (table 2).

Consumption of the complex of monosodium glutamate, sodium nitrite and Ponceau 4R on week 16 of the experiment led to the lowering of the mean values of the diameter of the lumen of the arteries of the submucous layer, accounting for $18.15 \pm 0.02 \mu\text{m}$, which was by 29.46 % and 2.2 % ($p < 0.05$) significantly lower than the values of the previous period of the experiment and values of the control group, respectively. The diameter of the venous lumen increased significantly by 27.5 % and 58.32 % ($p < 0.05$) compared to the resulting values on week 12 and values of the control group of rats, respectively. The mean values of the diameter of the venous lumen on week 16 were $45.09 \pm 0.07 \mu\text{m}$ (table 2).

Thus, the effect of the monosodium glutamate, sodium nitrite and Ponceau 4R complex food additives on the state of the vessels of the rat duodenum at the initial stages of the experiment led to the lowering of the mean values of the metric parameters of the vessels of the blood microcirculatory bed of the mucous membrane and dilatation of the lumen of the larger vessels of the submucous layer. Such reaction is obviously associated with the direct action of these substances on the mucous membrane, the vessels of which responded by narrowing the lumen, which in turn led to the dilatation of the lumen of the vessels of the submucous layer. This behavior can be compared with the effects of other exogenous factors studied earlier, namely, ethanol, under which the vessels of the blood microcirculatory bed responded by narrowing the lumen at the early stages of the experiment, which proves their direct effect on the state of the vascular bed [14], and other exogenous factors [13]. The analysis of the morphometric parameters and histological changes caused by the development of inflammatory response to the complex action of food additives, has established that the resistance and exchange vessels of the mucous membrane responded with a significant increase in lumen diameter, which led to edema of the mucous membrane, and the capacitance vessels were constricted due to compression of the adjacent tissues; eventually, these phenomena led to a decrease in the metric values of the diameter of the lumen of the vessels of the submucous layer, compared to the previous period of the experiment. Subsequently, in response to the effect of the complex of monosodium glutamate, sodium nitrite and Ponceau 4R due to the formation of compensatory-adaptive reactions of the body to the action of food additives, the values at the middle stage of the experiment were restored, which led to a decrease in the lumen diameters of the vessels of the resistance and exchange sections with dilatation of the diameter of the venules, which in turn provoked a significant imbalance between the two sections of the blood microcirculation bed, leading to dilatation of the lumen of arterioles and venules along with narrowing of the lumen of the exchange vessels of the mucous membrane and decrease in the diameter of the lumen of arteries with persistent dilatation of veins of the submucous layer at the end of the experiment. These phenomena led to disruption of blood perfusion through blood vessels, with occurrence of hypoxia and dystrophic lesions, which were preceded by inflammation of the mucous membrane with subsequent restoration of the values, though no complete normalization occurred due to prolonged and permanent impact of the complex food additives on the duodenal mucosa. The nature of the changes in the vessels of the submucous layer depended on the changes in the vessels of the mucous membrane during the experiment, which led to a narrowing of the lumen of the arteries and persistent venous dilatation.

Conclusion

The present morphometric study has found that the action of the complex food additives affects the state of the blood microcirculatory bed of the rat duodenal mucosa, which leads to changes in the hemodynamics of larger vessels of the submucous layer. At the early stages of observation, the lowering of the mean values of the metric parameters of the vessels of the blood microcirculatory bed of the mucous membrane, and dilatation of the lumen of larger vessels of the submucous layer, caused by the direct action of the above additives on the mucous membrane, was determined. Subsequently, the development of the inflammatory reaction with edema to the complex action of food additives led to a decrease in the diameters of the lumen of the resistance and exchange vessels with dilatation of the lumen of the venules, which in turn provoked a significant imbalance between two sections of the blood microcirculatory bed and disruption of blood perfusion and dystrophic lesions, followed by restoration of the values, due to compensatory-adaptive responses to the irritant, though no complete normalization occurred due to prolonged and persistent action of complex food additives on the duodenal mucosa.

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Стаття надійшла 24.02.2020 р.