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REACTIVE CHANGES IN THE VESSELS OF THE RAT'S CAECUM WALL MUCOSA AND SUBMUCOUS MEMBRANE IN RESPONSE TO THE EFFECT OF COMPLEX FOOD ADDITIVES

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The aim of the work was to determine the dynamics of changes in the metric parameters of the vessels of the mucous membrane of the wall of the cecum and the submucosa of rats in response to the action of complex food additives. The study was conducted on 84 sexually mature male rats. Rats of the control group were orally injected with physiological saline. Rats of the experimental group were orally administered 0.6 mg/kg of sodium nitrite, 20 mg/kg of monosodium glutamate, and 5 mg/kg of Ponceau 4R in 0.5 ml of distilled water once a day. The selection of samples for histological examination was carried out at 1, 4, 8, 12 and 16 weeks. It turned out that the use of food additives in a complex leads to a structural reorganization of the vessels of the mucous membrane and submucosa of the cecum of rats.

Key words: food additives, monosodium glutamate, sodium nitrite, ponceau 4R, rat.

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РЕАКТИВНІ ЗМІНИ В СУДИНАХ СЛИЗОВОЇ СТІНКИ СЛІПОЇ КИШКИ ТА ПІДСЛИЗОВОЇ ОБОЛОНКИ ЩУРІВ ПІД ВПЛИВОМ КОМПЛЕКСНИХ ХАРЧОВИХ ДОБАВОК

Метою роботи було визначити динаміку змін метричних параметрів судин слизової оболонки стінки сліпої кишки та підслизової оболонки щурів у відповідь на дію комплексних харчових добавок. Дослідження проводили на 84 статевозрілих самцях щурів. Щурам контрольної групи перорально вводили фізіологічний розчин. Щурам дослідної групи 1 раз на добу перорально вводили 0,6 мг/кг нітриту натрію, 20 мг/кг глутамату натрію та 5 мг/кг понсо 4R в 0,5 мл дистильованої води. Відбір зразків для гістологічного дослідження проводили на 1, 4, 8, 12 та 16 тижнях. Виявилось, що використання харчових добавок у комплексі призводить до структурної перебудови судин слизової оболонки та підслизової оболонки сліпої кишки щурів.

Ключові слова: харчові добавки, глутамат натрію, нітрит натрію, понсо 4R, щури.

The work 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.

Food additives are substances that are added to finished products or raw materials as preservatives, antimicrobials, flavor enhancers, and colorants. In other words, the addition of such compounds to products is provided by the technological process. However, not all food additives are harmless to consumer health. The minimum daily intake for most food additives is set by law. To conduct the experiment, we selected three food additives that have different purposes and are most often combined in food as preservatives, colorants, and flavor enhancers.

An analysis of the literature shows that most of the food additives authorized for use cause negative effects on the human and animal body. Recently, the issue of preventing the free sale of sodium nitrite has been raised more and more often. Poisoning with this substance leads to the development of methemoglobinemia and fatalities [7]. Sodium nitrite is added to meat products as a preservative, as well as to improve color and taste [13]. It has been proven that exposure to a complex of sodium nitrite and sodium glutamate causes changes in the lungs of pregnant female rats in the form of inflammatory and necrotic processes [2]. The complex of dietary supplements of sodium nitrate, potassium nitrite, benzoic acid, sorbic acid and monosodium glutamate affects iron metabolism, which leads to a decrease in the number of red blood cells, a decrease in hematocrit and hemoglobin [12]. When a complex of food coloring containing ponceau 4R is administered orally to pregnant female rats, changes in the structure of hippocampal proteins are detected in their offspring. The content of ponceau 4R and tartrazine in drugs used in pediatric practice is likely to cause frequent allergic reactions in children [10].

The purpose of the study was to determine the dynamics of changes in the metric parameters of the vessels of the rat's caecum wall mucosa and submucous membrane in response to the effect of complex food additives.

Materials and methods. The experiment involved 84 mature male rats (Rattus norvegicus) weighing 204.5±0.67 g, which were obtained from the experimental-biological clinic of the Poltava State Medical University. All procedures followed the standard rules established by the commission of Poltava State Medical University on ethical issues and bioethics (order of the rector No. 330 of May 30, 2020) in accordance with the European Communities Council Directive of 24 November 1986 (86/609/EEC). The rats of all groups had access to food and water ad libitum. The animals were sacrificed under thiopentone anesthesia overdose. The rats of control group (n=14) consumed drinking water and were administered with saline orally. The rats of the experimental group (n=70), with access to water ad libitum, were administered with 0.6 mg/kg sodium nitrite E250 (Uralchem, China), 20 mg/kg monosodium glutamate E621 (Multichem, China) and 5 mg/kg Ponceau 4R E124 (Multichem, China) in 0.5 ml of distilled water once daily orally. The hypothesis of the experiment was to establish the effect of food additives allowed in the food industry in doses twice smaller than those allowed in the complex. Collection of samples for histological examination was carried out at 1 (n=14), 4 (n=14), 8 (n=14), 12 (n=14) and 16 (n=14) weeks. After euthanasia the rats were dissected following the method of complete evisceration. The cecum was removed and fixed with a 10 % neutral formalin solution. The material was washed and prepared for paraffin embedding according to standard techniques [11]. Sections of 5-10 μm thick were obtained using the на manual rotary microtome HistoLine. Histological sections were stained with hematoxylin and eosin (H&E). Series of histological slide's photomicrographs from objectives 4x and 10x were captured by a microscope Levenhuk D740T attached to a digital 5.1 Mpx kit camera. Photo fixation and morphometry were performed in Levenhuk Lite software. Statistical calculations were performed using Microsoft Office Excel with the Real Statistics extension. To check the distribution for normality, the calculation of the Shapiro-Wilk test was applied. 57 If the variation series corresponded to a normal distribution, then the Student's t-test for independent samples was used to compare them. Besides, $p<0.05$ was considered to be statistically significant. In the case when the series of results were not subject to normal distribution, statistical processing was carried out using a non-parametric method – the Mann-Whitney U-test.

Results of the study and their discussion. According to the results of morphometric studies of the vessels of the mucous membrane of the control group of rats, it was found that the lumen diameter of arterioles was 11.15±0.21 μm, capillaries – 4.8±0.14 μm, venules – 14.5±0.27 μm (Table 1, Fig. 1).

Table 1

Morphometric characteristics of the vessel diameter of the mucous membrane of the rat cecum (M ± m)

Term, weeks	Vessel diameter of the mucous membrane, μm		
	Arterioles	Capillaries	Venules
Control group (n=14)	11.15±0.21	4.8±0.14	14.5±0.27
1 (n=14)	13.05±0.18*	5.13±0.04*	15.55±0.39*
4 (n=14)	9.79±0.16*,**	4.03±0.05*,**	10.32±0.14*,**
8 (n=14)	11.32±0.28**	4.37±0.08 *,**	14.35±0.12**
12 (n=14)	12.79±0.21*,**	4.14±0.91	13.48±0.2*,**
16 (n=14)	12.59±0.16*	5.56±0.66	13.46±0.17*

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

At the 1st week of the experiment, the lumen diameter of the mucosal arterioles was 13.05±0.18 μm, which was significantly higher than the control values by 13.47 %. The diameter of the lumen of the mucosal capillaries was 5.13±0.04 μm, which was significantly higher than the control results by 6.88 %. The diameter of the lumen of the mucosal venules was 15.55±0.39 μm, which was 7.24 % significantly higher than the control (Fig. 1).

According to the results of morphometric studies of the mucous membrane of the rat cecum at week 4 of the experiment, it was found that the diameter of the arteriolar lumen was 9.79±0.16 μm. This index was significantly lower than the results of the control group and the results of the previous observation period by 14.86 % and 24.98 %, respectively. The diameter of the lumen of the mucosal capillaries was 4.03±0.05 μm, which is 16.04 % less than in the control group and 21.44 % less than in the previous follow-up period. The diameter of the lumen of the mucosal venules was significantly smaller than that of the control group and the previous observation period by 28.83 % and 33.63 %, respectively, and amounted to 10.32±0.14 μm.

At the 8th week of the experiment, the diameter of the lumen of the mucosal arterioles was 11.32±0.28 μm, which was significantly higher by 15.63 % compared to the results of the previous observation period. The diameter of the lumen of the mucosal capillaries was 4.37±0.08 μm. These values

were significantly lower than the control by 13.75 % and at the same time higher than the results of the 4th week of the experiment. The diameter of the lumen of the mucosal venules was 14.35±0.12 µm and was significantly higher than the previous observation period by 39.05 %.

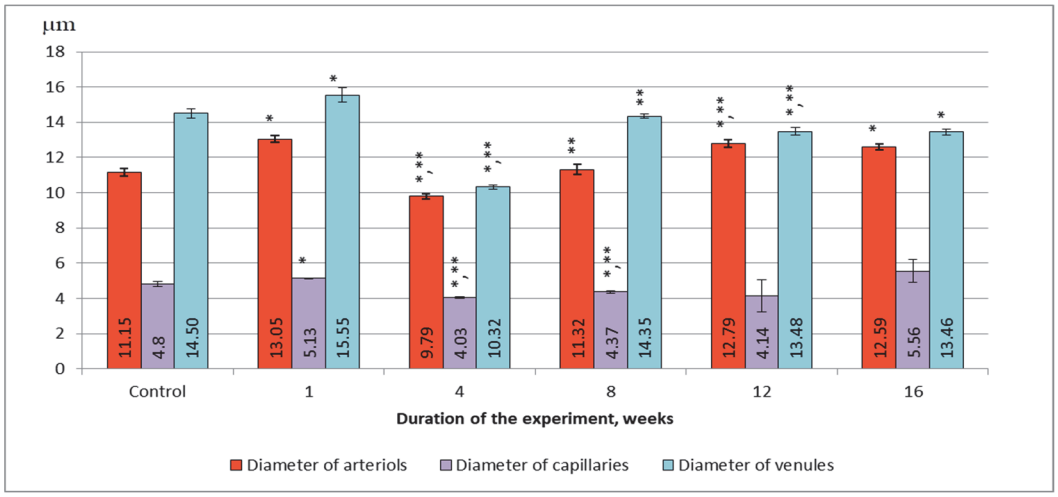

Fig.1. Dynamics of morphometric characteristics of vessel diameter in the mucous membrane of the rat cecum.

According to the results of morphometric studies of the mucous membrane of the rat cecum at the 12th week of the experiment, it was found that the diameter of the arteriolar lumen was 12.79±0.21 µm. This result was significantly higher than the control and 8th week of observation by 8.7 % and 12.98 %, respectively. The diameter of the lumen of the mucosal capillaries was 4.14±0.91 µm and did not differ significantly from the results of the control and the previous observation period. The lumen diameter of the mucosal venules was within 13.48±0.2 µm. This result was significantly lower compared to the control and the results of the 8th week of observation by 7.03 % and 6.06 %, respectively.

At the 16th week of the experiment, the diameter of the lumen of the mucosal arterioles was 12.59±0.16 µm, which was significantly higher than in the control by 12.91 %. The diameter of the lumen of the mucosal capillaries reached 5.56±0.66 µm and did not differ significantly from the results of the control and the 8th week of observation. The diameter of the lumen of the mucosal venules was 13.46±0.17 µm and was significantly less than in the control group by 7.17 %.

Morphometric studies of the submucosal base of the mucous membrane of the rat cecum revealed that the diameter of the lumen of arteries was 24.85±0.56 µm, arterioles – 12.03±0.32 µm, capillaries – 4.77±0.19 µm, venules – 16.3±0.87 µm, and veins – 39.43±0.75 µm (Table 2, Fig. 2).

Table 2

Morphometric characteristics of the diameter of the vessels of the submucosal base of the rat cecum (M ± m)

Term, weeks	Diameter of the submucosal vessels, µm				
	Arteries	Arterioles	Capillaries	Venules	Veins
Control group (n=14)	24.85±0.56	12.03±0.32	4.77±0.19	16.3±0.87	39.43±0.75
1 (n=14)	21.07±0.17*	9.32±0.14 *	4.93±0.1	15.34±0.16	38.85±1.2
4 (n=14)	20.57±0.2*,**	9.88±0.15*,**	3.95±0.06*,**	14.17±0.16*,**	33.67±0.62*,**
8 (n=14)	23.22±1.03	9.44±0.13*,**	3.83±0.05*,**	16.29±0.28**	36.16±0.65*,**
12 (n=14)	16.79±0.28*,**	10.61±0.16*,**	5.07±0.71**	13.43±0.18*,**	32.94±0.85*,**
16 (n=14)	26.73±0.49*,**	14.4±0.08*,**	5.35±0.39	13.28±0.1*	34.03±1.0*

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

At the 1st week of the experiment, the diameter of the lumen of the arteries of the submucosal base of the intestine was 21.07±0.17 µm, which was 15.21 % significantly lower compared to the result of the control group. The diameter of the lumen of the arterioles of the submucosa was 9.32±0.14 µm, which was significantly lower than in the control group by 22.53 %. The diameter of capillaries was 4.93±0.1 µm, venules – 15.34±0.16 µm and submucosal veins – 38.85±1.2 µm. These indices did not differ significantly from the results of the control group.

At the 4th week of the experiment, the diameter of the lumen of the submucosal arteries was 20.57±0.2 µm, which is significantly less than the control group and the results of week 1 of the experiment by 17.22 % and 2.37 %, respectively. The arteriolar diameter of the submucosal base was 9.88±0.15 µm. This result was 17.87 % significantly less than the control and 6.01 % more than the previous observation period.

The diameter of the submucosal capillaries was 3.95±0.06 μm, which was 17.19 % less than in the control group and 20.28 % less than in the 1st week of follow-up. The diameter of the submucosal venules was within 14.17±0.16 μm and was significantly less than the results of the control and the previous observation period – by 13.05 % and 7.62 %, respectively. The diameter of the lumen of the submucosal veins was 33.67±0.62 μm. This index was significantly lower compared to the results of the control group by 14.61 % and at the same time significantly higher by 13.33 % compared to the results of the 1st week of the experiment.

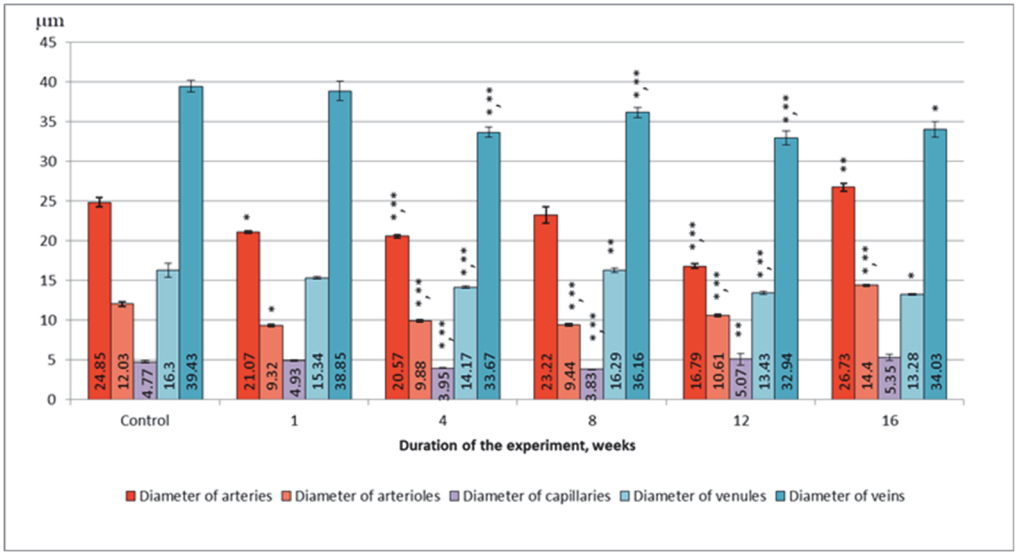

Fig.2. Dynamics of morphometric characteristics of vessel diameter in the submucosal base of the rat cecum.

At the 8th week of the experiment, the diameter of the arteries of the submucosa was within 23.22±1.03 μm and did not differ significantly from the results of the control group and the results of the previous period. The diameter of the lumen of the arterioles of the submucosa was 9.44±0.13 μm, which was significantly less than the results of the control group and the 4th week of the experiment by 21.53 % and 4.45 %, respectively. The diameter of the lumen of the submucosal capillaries was 3.83±0.05 μm, this result was significantly less by 19.71 % compared to the control and by 3.04 % compared to the previous observation period. The diameter of the lumen of the submucosal venules was 16.29±0.28 μm, which was significantly more than the results of the 4th week of observation by 14.96 %. The diameter of the lumen of the submucosal veins was 36.16±0.65 μm. It was found that this result was 8.29 % less than the control, and 7.4 % more than the previous observation period.

At the 12th week of the experiment, the diameter of the lumen of the arteries of the submucosal base of the rat cecum was within 16.79±0.28 μm. The result was significantly lower compared to the control group and the results of the previous observation period by 32.43 % and 27.69 %, respectively. The diameter of the lumen of the arterioles of the submucosal base was 10.61±0.16 μm and was significantly smaller than in the control group by 11.8 %. However, at this time, there was an increase in the diameter of the arterioles of the submucosa compared to the 8th week of observation by 12.39 %. The lumen diameter of the submucosal capillaries was within 5.07±0.71 μm. This result was significantly higher than the previous observation period by 32.38 %, however, it did not have a significant difference with the control. The lumen diameter of the submucosal venules was 13.43±0.18 μm. At this time, the lumen diameter of the submucosal venules was significantly smaller than that of the control and the previous observation period by 17.61 % and 17.56 %, respectively. The diameter of the submucosal veins was within 32.94±0.85 μm. The result was significantly lower than the results of the control group by 16.46 %, and also relative to the 8th week of observation – by 8.9 %.

At the 16th week of the experiment, the diameter of the arteries of the submucosal base was 26.73±0.49 μm, which was 7.57 % more than in the control. This indicator increased significantly by 59.2 % compared to the 12th week of observation. The lumen diameter of the submucosal arterioles was 14.4±0.08 μm, this result was significantly higher than the control and the results of the previous follow-up period by 19.7 % and 35.72 %, respectively. The value of the diameter of the lumen of the submucosal capillaries was 5.35±0.39 μm and did not differ significantly from the control and previous observation periods. The diameter of the venules of the submucosa was 13.28±0.1 μm and significantly decreased compared to the control by 18.53 %. The diameter of the lumen of the submucosal veins was 34.03±1.0 μm, which was significantly less than the control values by 13.7 %.

The wall of the cecum, and in particular, its mucous membrane, has a well-developed system of microcirculatory vessels (MCV). This feature is due to the functions of the mucous membrane of the large intestine – ensuring the absorption of water and electrolytes. The regulation of the cecum's MCV is complex. The walls of the blood vessels of the cecum contain receptors of the renin-angiotensin system, which regulates the transport of water and sodium [5]. It has been established that reparative angiogenesis of the small intestinal mucosa is impaired in the presence of inflammatory processes and dysbiosis [6]. The results of morphometric studies of the vessels of the mucous membrane and submucosal base of the rat cecum indicate pronounced changes in the diameter of the lumen of the vessels of the metabolic and resistive links. A number of authors have reported on the effects of food additives such as monosodium glutamate, sodium nitrite, and ponceau 4R on blood vessels of various calibers. Under the conditions of sodium glutamate, sodium nitrite, and ponceau 4R administration in combination, hemodynamic disorders in the vessels of the microcirculatory bed of the adrenal cortex of rats are observed [3]. Thus, at the 1st week of the experiment, there is a sharp dilation of the arterioles of the mucous membrane of the cecum, followed by their spasm at the 8th week. Repeated dilation of arterioles to values that were significantly higher than the control values occurred at the 16th week of observation. The results of the study are consistent with the data of Hagihara GN et al. (2014). It was found that in rats with sodium glutamate-induced obesity, dilatation of mesenteric arteries was observed due to impaired interaction of endothelial receptors with angiotensin II [4]. We recorded a similar reaction of the mucosal capillaries. At the 1st week of consumption of the complex of food additives, there is a sharp expansion of the lumen of the mucous membrane capillaries, then their lumen narrows from the 4th to the 8th week. By the 16th week of the experiment, the lumen of capillaries increases to values that do not differ significantly from those of the control group. The diameter of the lumen of the mucosal venules changes similarly. At the 1st week of the experiment, there is an increase in the lumen of the venules, followed by their spasm at the 4th week of observation. At the 8th week of observation, there is a sharp dilation of the venular lumen, and then its re-narrowing. Thus, the sharp dilation and subsequent narrowing of the lumen of the vessels of the metabolic link can be explained by the increasing inflammatory process and edema, which causes venous dilation. Incomplete restoration of the diameter of the vessel lumen to the level of the control group at late follow-up is likely due to compensatory and adaptive mechanisms in response to the action of an altering factor, which is a complex of food additives [15].

At the 1st and 4th weeks of observation, spasm of the submucosal arteries occurs, followed by dilation to the control level at the 8th week of the experiment. A sharp spasm of the arterial lumen at week 12 and their repeated dilation was observed at week 16 of the experiment. The diameter of the submucosal arterioles was significantly smaller than in the control group during 12 weeks of the experiment. Significant dilatation of arterioles relative to the control values occurs at the 16th week of the experiment. Majewski M et al (2018) found that the administration of sodium glutamate changes the response of vascular smooth muscle, which also likely causes an increase in blood pressure in experimental rats in a short-term experiment [8]. It can be assumed that the spasm of arteries and arterioles of the mucous membrane is caused by the effect of sodium glutamate on vascular smooth muscle cells. Further dilation of the arteries and arterioles of the submucosa can be interpreted as a compensatory reaction or a disruption of the interaction of endothelial receptors with angiotensin II under conditions of prolonged exposure to food additives [4]. It has been reported that rats treated with sodium glutamate in the form of subcutaneous injections showed a decrease in the ratio of aortic wall thickness to lumen diameter [7]. It has also been proven that exposure to a complex of sodium nitrite and sodium glutamate causes hypoplasia of muscle fibers around blood vessels in the lungs of pregnant female rats when observed for 15 days [2]. This again confirms the hypothesis of a change in the diameter of arteries and arterioles due to the interaction of vascular smooth muscle cells with sodium glutamate. A pronounced reaction of the submucosal capillaries in the form of spasm was observed only at weeks 4 and 8 of the experiment. At the 12th week of observation, the capillary lumen dilated relative to the previous observation period. At the same time, the indicators of the last, 16th week do not have a significant difference from the control and the results of the 12th week of the experiment. Nakadate K et al. (2015) also reported that sodium glutamate consumption in rats causes dilatation of hepatic sinusoidal capillaries [9]. The diameter of the venules of the submucosal base significantly decreased starting from the 1st week of the experiment. At the 8th week of observation, dilatation of venules was recorded, which was replaced by spasm at the 12th week of the experiment, which persisted until the end of the experiment. The diameter of the lumen of the submucosal veins at the beginning of the experiment did not change significantly compared to the control. Subsequently, there is a sequential dilatation and spasm of the submucosal veins at the 8th and 12th weeks of observation,

respectively. At the end of the experiment, the veins were still in a spasmodic state, their lumen was significantly smaller than in the control group at week 16. Thus, the direct effect of the complex of food additives causes hemodynamic disorders in the vessels of the resistive, capacitive and metabolic links of both the mucous membrane and the submucosal base. The development of an inflammatory reaction and tissue hypoxia triggers a cascade of compensatory and recovery reactions. However, complete recovery does not occur, as the effect of the altering factor continues.

The blood vessels of mucous membranes are extremely sensitive to various chemical stimuli. We assume that the reaction of microcirculatory vessels in response to the presence of an altering factor is universal. Thus, under chronic ethanol intoxication in the vessels of the microcirculatory bed of the salivary glands, a sharp dilatation of the vessels was also observed, followed by narrowing and partial restoration of the diameter at the end of the experiment [14]. At the same time, the vessels of both the resistive and capacitive links react consistently.

Conclusion

The use of food additives in the complex caused a vascular reaction of the vessels of the mucous membrane and submucosa of the rat cecum. In the mucous membrane, arterioles reacted with dilatation on 13.47 % during the first week of observation, and by the fourth week a spasm was formed on 24.98 %. By the 12th week of observation, the value of the lumen of the arterioles reliably exceeded the control by 8.7 %, which was due to the development of compensatory and restorative processes aimed at restoring blood perfusion in the hemomicrocirculatory channel of the mucous membrane. The metabolic link in the mucous membrane maximally reduced the lumen diameter during the fourth to eighth week on 16.04 % and 13.75 % reliably, which is associated with hyperhydration of the surrounding connective tissue; from the twelfth week, blood flow gradually recovered. In the venules, the minimum values were characterized by the fourth week of the experiment, again due to hyperhydration during this period of the experiment. In the submucosa, the changes correlated with the trends in the mucosa. The lumen diameter values were minimal at the fourth week of observation, followed by a recovery to the control group of animals.

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