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MORPHOLOGICAL AND METRIC CHANGES OF THE GLANDULAR APPARATUS OF THE RAT STOMACH FUNDUS UNDER THE EFFECT OF A COMPLEX OF FOOD ADDITIVES

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The paper presents the data of morphometric and histological examination in the complex action of food additives on the glandular apparatus of the stomach fundus. It was found that the complex action of dietary supplements of sodium nitrite, sodium glutamate and Ponceau 4R leads to changes in morphometric parameters of the fundus glands with the development of a complex reaction, followed by inflammatory reaction and edema. Reconstructive reactions aimed at neutralizing the alternative factor and restoring the morphofunctional state of the glands of the stomach fundus do not lead to complete recovery of structural components due to the predominance of constant negative stimuli with dystrophic changes, expressed by changes in morphometric parameters and morphological structure.

Key words: fundus of the stomach, food supplements, rats.

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МОРФОЛОГІЧНІ І МЕТРИЧНІ ЗМІНИ ЗАЛОЗИСТОГО АПАРАТУ ФУНДАЛЬНОГО ВІДДІЛУ ШЛУНКУ ЩУРІВ ПІСЛЯ ДІЇ КОМПЛЕКСУ ХАРЧОВИХ ДОБАВОК

В роботі представлені дані морфометричного та гістологічного дослідження при комплексній дії харчових добавок на залозистий апарат фундального відділу шлунка. Встановлено, що комплексна дія харчових добавок нітриту натрію, глутамату натрію та Понсо 4R призводить до змін морфометричних показників залоз фундального відділу з розвитком складної, комплексної реакції, з послідовною запальною реакцією та набряком. Відновно-приспосувальні реакції спрямовані на знешкодження альтеративного фактору та на відновлення морфофункціонального стану залоз фундального відділу шлунка не призводять до повного відновлення структурних компонентів, внаслідок переважання постійного негативного впливу подразника з виникненням дистрофічних змін, що виражається зміною морфометричних показників та морфологічної структури.

Ключові слова: фундальний відділ шлунку, харчові добавки, щури.

The stomach, being the essential organ of the digestive system with its proper structural features and performing a number of important functions, namely, excretory, endocrine, absorptive, neutralizing, mechanical, Castle's antianemic factor production, is one of the organs of the digestive system, which is affected first under the various critical states [2, 8]. The experimental studies report that the digestive system of humans and rats is a homologous functional system that has much in common in terms of the structure and function of organs [3, 7].

Due to the increasing demand for food in modern society, manufacturers use different types of food additives, and the study of the harmful effects of their chemical components on organs and systems of the body is very up-to-date and remains open [9].

The analysis of the content of food additives in domestic and foreign products showed that the most common additives are monosodium glutamate, sodium nitrite and synthetic dye Ponceau 4R [4, 5, 6, 9, 10, 12, 15]. Thus, the issue of the effect of food additives on the body is currently relevant, such studies are extremely important for developing a scientifically sound strategy to increase tolerance of humans, and animals to xenobiotics by activating genetically engineered mechanisms and creating the new perfect adaptogens.

The purpose of the study was to establish the dynamics of changes in the metric parameters of the structural components of the glands of the rat stomach fundus mucosa in normal condition and under the effect of the complex of food additives, namely, monosodium glutamate, sodium nitrite and Ponceau-4R.

Material and methods. 84 outbred mature male rats were involved in the study. The control group of rats consumed drinking water and additionally received saline per os. The rats of the experimental group had access to water ad libitum and 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 a day per os. The doses of food additives were half lower than the allowable normal rate in food products. Prior euthanasia, the rats' adaptive behaviour was evaluated using the "open field" test [13] with subsequent processing of the resulting data using the methods of variation statistics with Excel software [1].

The animals were sacrificed within 1, 4, 8, 12 and 16 weeks under thiopentone anesthesia overdose. Upon euthanasia, the part of the fragments of the stomach fundus wall was fixed in 10 % neutral formalin solution for three days and the rest fragments in 2.5 % glutaraldehyde solution. Subsequently, the pieces of the stomach wall, fixed in formalin, were embedded into paraffin and epon [11]. The slices were obtained using the sledge microtome and ultramicrotome and mounted on the slides. Staining was performed with hematoxylin and eosin, toluidine blue and polychrome dye; the slices were enclosed in polystyrene and studied in the light microscope. Microimaging and the morphometric study was made using the digital microscope equipped with DCM 900 digital micro photo attachment and software, adapted to the studies. Statistical processing of morphometric data was made using Excel software [1].

Results of the study and their discussion. The findings of the morphometric study of the bottom of the gastric glands of the stomach fundus of control rats showed that the outer and inner diameter was 29.53 ± 0.23 μm and 4.81 ± 0.07 μm , respectively, and the height of epitheliocytes was 9.89 ± 0.16 μm (Table 1).

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Morphometric parameters of the bottom of the glands of rat stomach fundus

Parameters	The bottom of the gland (μm)		
	The outer diameter	The inner diameter	The height of epitheliocytes
Control	29.53 ± 0.23	4.81 ± 0.07	9.89 ± 0.16
Week 1	28.20 ± 0.10 *	4.02 ± 0.06 *	11.62 ± 0.09 *
Week 4	52.03 ± 0.24 * **	3.28 ± 0.03 * **	14.06 ± 0.09 * **
Week 8	39.69 ± 0.15 * **	4.36 ± 0.06 * **	10.51 ± 0.06 * **
Week 12	34.65 ± 0.08 * **	4.23 ± 0.04 * **	13.20 ± 0.10 * **
Week 16	39.31 ± 0.13 * **	6.02 ± 0.12 * **	11.96 ± 0.09 * **

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

On week 1, the consumption of complex of the food additives led to a decrease in the mean values of the outer and inner diameter of the fundic glands by 4.72 % and 16.42 % ($p < 0.05$), respectively, accounting for 28.20 ± 0.10 μm and 4.02 ± 0.06 μm , respectively; the height of epitheliocytes was by 17.49 % greater compared to controls, accounting for 11.62 ± 0.09 μm ($p < 0.05$).

On week 4, the consumption of monosodium glutamate, sodium nitrite and Ponceau 4R led to an increase in the outer diameter of the fundic glands by 84.50 %, compared to the previous period of the experiment, accounting for 52.03 ± 0.24 μm , that was by 76.19 % significantly greater compared to controls ($p < 0.05$). On week 4 the inner diameter was 3.28 ± 0.03 μm , which was by 18.41 % significantly lower compared to the values of the previous period of the experiment and by 31.81 % lower compared to controls ($p < 0.05$). The height of epitheliocytes increased both by 21.00 %, compared to the values of week 1 and by 42.16 %, compared to controls, accounting for 14.06 ± 0.09 μm ($p < 0.05$).

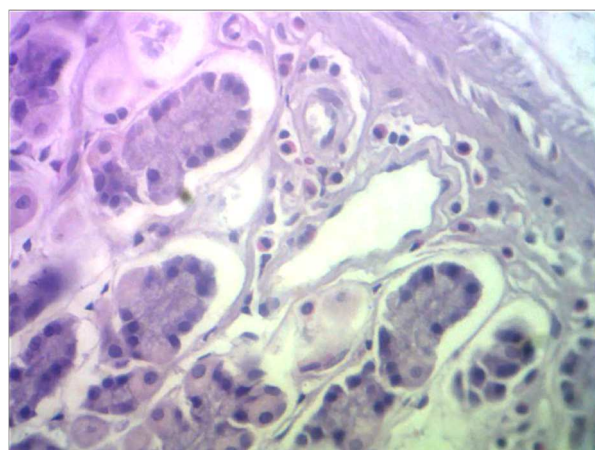


Fig. 1. Detachment of the basement membrane in the area of the bottom of the glands of the rat stomach fundus on week 4 of the experiment. H&E stain. Ocular lens: 10×magnification, objective lens: 40×magnification.

The structure of the fundic glands of the stomach was simple, tubular, with a somewhat moderately long body, and a flattened bottom. On histological specimens, the basal plasmalemma lost contact with the basement membrane, resulting in the detachment of the latter with excess fluid from the mucosal lamina propria, which was defined as hyperhydrated, which determined an increase in the diameter of the outer bottom of the fundic glands. No hemocytes were detected in the vessels. No signs of epitheliocyte desquamation were noted. The nuclei were located in the basal part of the exocrinocytes. The lumens of the glands were narrowed. Numerous leukocytes were detected in the lamina propria (fig. 1).

On week 8, the combined effect of the food additive led to a decrease in the mean values of the outer diameter by 23.72 %, accounting for 39.69 ± 0.15 μm ; however, they were by 34.41 % significantly greater compared to controls ($p < 0.05$). The mean values of the diameter of the fundic glands' lumen were 4.36 ± 0.06 μm , that was by 32.93 % significantly greater compared to the values on week 4 and by 9.36 %

significantly lower compared to controls ($p < 0.05$). The height of epitheliocytes was by 25.25 % significantly lower compared to the values of the previous period of the experiment, accounting $10.51 \pm 0.06 \mu\text{m}$ and by 6.27 % significantly greater compared to controls ($p < 0.05$).

On week 12, the combined effect of the food additives led to decrease in the outer diameter of the fundic glands by 12.70 %, compared to the values of the previous period of the experiment, accounting for $34.65 \pm 0.08 \mu\text{m}$, that was by 17.34 % significantly greater compared to controls ($p < 0.05$). The mean values of the inner diameter decreased both by 2.98 %, compared to week 8 and by 12.05 %, compared to controls, accounting for $4.23 \pm 0.04 \mu\text{m}$ ($p < 0.05$). The height of epitheliocytes was by 25.59 % significantly greater compared to the previous period of experiment and by 33.47 % greater compared to the controls, accounting for $13.20 \pm 0.10 \mu\text{m}$ ($p < 0.05$) on week 12 of the experiment.

Following 16 weeks of the combined effect of a complex of the food additives the outer diameter of the fundic glands increased by 13.45 %, accounting for $39.31 \pm 0.13 \mu\text{m}$, which was by 33.12 % significantly greater compared to the controls ($p < 0.05$). The mean values of the inner diameter were also by 42.32 % significantly greater compared to the values of the previous period of the experiment, accounting for $6.02 \pm 0.12 \mu\text{m}$, and by 25.16 % greater compared to the controls ($p < 0.05$). The height of epitheliocytes was $11.96 \pm 0.09 \mu\text{m}$, which was by 9.39 % significantly greater compared to the values on week 12 of the experiment and by 20.93 % greater compared to the controls, accounting for $11.96 \pm 0.09 \mu\text{m}$ ($p < 0.05$).

The findings of the morphometric study of the body of the fundic glands showed that the mean values of the outer and inner diameter was $29.38 \pm 0.22 \mu\text{m}$ and $6.52 \pm 0.05 \mu\text{m}$, respectively, and the height of epitheliocytes was $11.67 \pm 0.11 \mu\text{m}$ (table 2).

Table 2

Morphometric parameters of the body of the glands of rat stomach fundus

Parameters	The body of the gland (μm)		
	The outer diameter	The inner diameter	The height of epitheliocytes
Control	29.38 ± 0.22	6.52 ± 0.05	11.67 ± 0.11
Week 1	35.53 ± 0.20 *	6.96 ± 0.07 *	14.44 ± 0.08 *
Week 4	26.27 ± 0.08 *,**	10.78 ± 0.09 *,**	8.33 ± 0.07 *,**
Week 8	28.64 ± 0.19 *,**	7.18 ± 0.06 *,**	10.05 ± 0.06 *,**
Week 12	30.71 ± 0.05 *,**	4.94 ± 0.06 *,**	10.97 ± 0.09 *,**
Week 16	37.38 ± 0.20 *,**	8.36 ± 0.11 *,**	10.42 ± 0.14 *,**

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 consumption of complex of food additives the body of the fundic glands responded with the increase in the outer and inner diameters by 20.93 % and 6.75 %, respectively, accounting for $35.53 \pm 0.20 \mu\text{m}$ and $6.96 \pm 0.07 \mu\text{m}$, respectively, and the height of epitheliocytes was $14.44 \pm 0.08 \mu\text{m}$, that was by 23.74 % significantly greater, compared to controls ($p < 0.05$).

Following the 4 weeks of the consumption of monosodium glutamate, sodium nitrite and Ponceau 4R the outer diameter of the body of the fundic glands was $26.27 \pm 0.08 \mu\text{m}$, that was by 26.02 % significantly lower compared to the values of the previous period of the experiment and by 10.59 % significantly lower compared to controls ($p < 0.05$). The mean values of the inner diameter of the body of the glands were by 54.89 % significantly greater compared to the values on week 1 of the experiment and by 34.66 % greater compared to controls, accounting for $10.78 \pm 0.09 \mu\text{m}$ ($p < 0.05$). The values of the height of epitheliocytes were by 42.31 % significantly lower compared to the values of the previous period of the experiment and by 28.62 % lower compared to controls, accounting for $8.33 \pm 0.07 \mu\text{m}$ ($p < 0.05$) on week 4 of the experiment.

When exposed to pollutants on week 8, the rat gastric mucosa responded by the mean values of the outer diameter of the body of the fundic glands, accounting for $28.64 \pm 0.19 \mu\text{m}$, that was by 9.02 % significantly greater compared to the previous period of the experiment, and by 2.52 % lower compared to controls ($p < 0.05$). The diameter of the lumen was by 33.40 % significantly lower compared to the values on week 4, accounting for $7.18 \pm 0.06 \mu\text{m}$, and was by 10.62 % significantly greater compared to controls ($p < 0.05$). The height of the epithelial cells was by 20.65 % significantly greater compared to the previous period of the experiment, though it was by 13.88 % lower than the value in the control group, accounting for $10.05 \pm 0.06 \mu\text{m}$ ($p < 0.05$).

Histological study showed destructive lesions, which were primarily caused by microcirculation disorders and, as a consequence, tissue hypoxia. The cytoplasm of exocrinocytes was compacted and homogenized. Nuclei in the center of the cytoplasm showed polymorphism. The basal plasmalemma lost

contact with the basement membrane due to the detachment of the latter with excess fluid from the mucosal lamina propria. Vacuoles of different sizes were found in the cytoplasm of individual cells (fig. 2a).

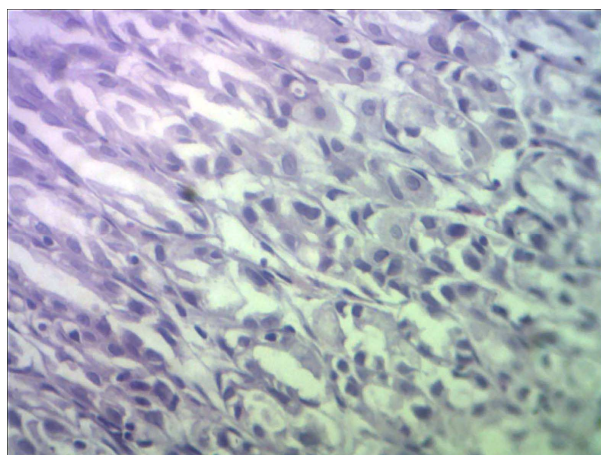


Fig. 2a. Vacuolization of the cytoplasm in the area of the body of the rat fundic glands on week 8 of the experiment. H&E stain. Ocular lens: 10x magnification, objective lens: 40x magnification.

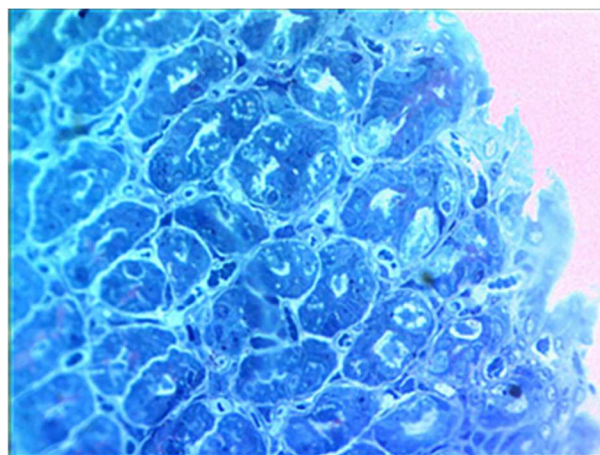


Fig. 2b. Dystrophic phenomena in the body of the rat fundic glands on week 16 of the experiment. Polychrome stain. Ocular lens: 10x magnification, objective lens: 40x magnification.

On week 12 of the consumption of complex of the food additives, the outer diameter of the fundic glands was $30.71 \pm 0.05 \mu\text{m}$, that was by 7.23 % significantly greater compared to the previous period of the experiment and by 4.23 % greater compared to the controls ($p < 0.05$). The mean values of the outer diameter were $4.94 \pm 0.06 \mu\text{m}$, which was by 31.20 % lower compared to the values on week 8 and by 24.43 % lower the values of the controls ($p < 0.05$). The height of epitheliocytes was by 9.15 % significantly greater compared to the previous period of the experiment and accounted for $10.97 \pm 0.09 \mu\text{m}$, though it was by 6.00 % significantly lower compared to the controls ($p < 0.05$).

At the end of the experiment, the mean values of the outer diameter were by 21.72 % greater compared to the previous period of the experiment and by 27.23 % greater compared to controls, accounting for $37.38 \pm 0.20 \mu\text{m}$ ($p < 0.05$). The inner diameter of the fundic glands was also by 69.97 % significantly greater compared to the values on week 12 of the experiment and by 28.22 % significantly greater compared to the controls, accounting for $8.36 \pm 0.11 \mu\text{m}$ ($p < 0.05$). The values of the epitheliocytes' height were $10.42 \pm 0.14 \mu\text{m}$, that was by 5.01 % significantly lower compared to the values of the previous period of the experiment and by 10.71 % lower compared to the controls ($p < 0.05$).

In the single-layer prismatic glandular epithelium of the stomach fundus, intensification of dystrophic lesions and occurrence of destructive changes were established. A progressive decrease in the secretory granules was noted; in the apical cytoplasm the areas of desolation were detected, which formed evaginations, separated from the epitheliocytes in the lumen of the stomach. Intensified morphological manifestations of secretion disorders were noted in the body of the fundic glands. The amount of condensed chromatin in the nuclei of oblong exocrinocytes increased. A small number of vacuoles of different diameters were determined in the cytoplasm (fig. 2b).

The findings of the morphometric study of the neck of the fundic glands established that the mean values of the outer and inner diameter were $22.46 \pm 0.07 \mu\text{m}$ and $6.75 \pm 0.03 \mu\text{m}$, respectively, and the height of epitheliocytes was $8.20 \pm 0.05 \mu\text{m}$ (table 3).

□□b□3

Morphometric parameters of the neck of the glands of rat stomach fundus

Parameters	The neck of the gland (μm)		
	The outer diameter	The inner diameter	The height of epitheliocytes
Control	22.46 ± 0.07	6.75 ± 0.03	8.20 ± 0.05
Week 1	25.54 ± 0.08 *	5.23 ± 0.04 *	10.95 ± 0.09 *
Week 4	29.77 ± 0.24 * **	10.66 ± 0.15 *	8.95 ± 0.10 * **
Week 8	32.38 ± 0.14 * **	10.87 ± 0.08 * **	11.12 ± 0.16 * **
Week 12	34.23 ± 0.08 * **	10.33 ± 0.06 * **	11.70 ± 0.08 * **
Week 16	28.62 ± 0.15 * **	7.80 ± 0.12 * **	11.47 ± 0.18 * **

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

The excretory ducts in the area of the neck of the glands were lined with prismatic epitheliocytes, the nuclei of which had a flattened shape and were located mainly in the basal part. The cytoplasm was clear and showed granules, which gave a γ -reaction when stained with toluidine blue. Isolated main and parietal exocrinocytes, as well as gastrointestinal endocrinocytes, were noted in the neck of the fundic glands. The specimen showed poorly differentiated cells with small dark nuclei, and a large number of mucocytes, the internal contents of which stained red. The vessels of the hemomicrocirculatory bed were represented by capillaries, which are morphologically represented by capillaries of the fenestrated type (fig. 3a).

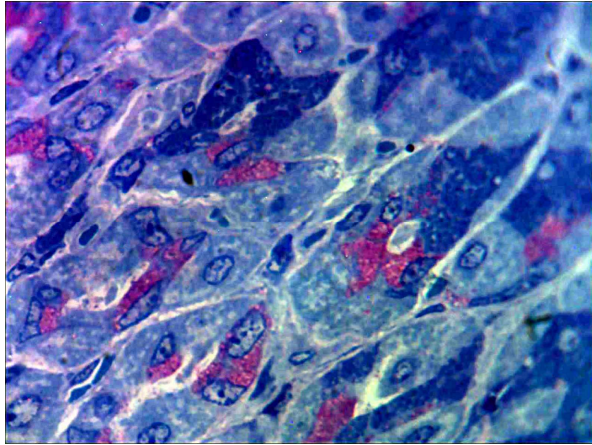


Fig. 3a. The area of the neck of the fundic glands of control rats. Toluidine blue stain. Ocular lens: 10×magnification, objective lens: 40×magnification.

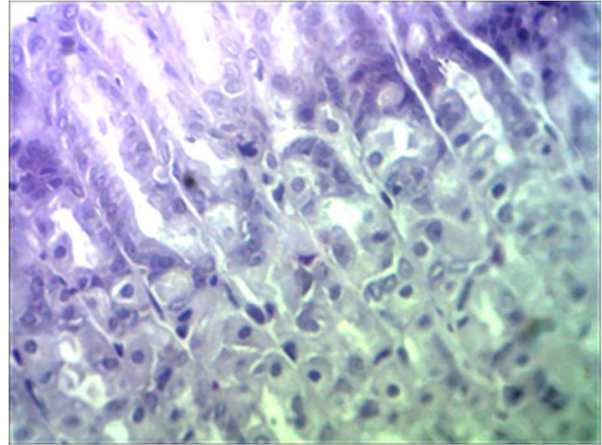


Fig. 3b. The phenomena of desquamation of cervical epitheliocytes of the glands of the rat stomach fundus on week 12 of the experiment. H&E stain. Ocular lens: 10×magnification, objective lens: 40×magnification.

On week 1 of consumption of complex of the food additives the outer diameter was $25.54 \pm 0.08 \mu\text{m}$, that was by 13.71 % significantly greater compared to the controls ($p < 0.05$). The mean values of the inner diameter, on the contrary, were by 22.52 % significantly lower compared to the control values, accounting for $5.23 \pm 0.04 \mu\text{m}$ ($p < 0.05$). The height of epitheliocytes was by 33.54 % greater compared to the controls, accounting for $10.95 \pm 0.09 \mu\text{m}$ ($p < 0.05$).

Following the 4 weeks of consumption of complex of the pollutants, the outer diameter of the neck of the fundic glands was by 16.56 % significantly greater compared to the parameter of the previous period of the experiment and by 32.55 % greater compared to the controls, accounting for $29.77 \pm 0.24 \mu\text{m}$ ($p < 0.05$). The value of the inner diameter increased significantly by 103.82 % and 57.93 %, compared to the values on week 1 of the experiment and values of control group of animals, respectively, accounting for $10.66 \pm 0.15 \mu\text{m}$ ($p < 0.05$). The height of epitheliocytes was 18.26 % significantly lower compared to the values of the previous period of the experiment, though it was by 9.15 % significantly lower compared to the controls, accounting for $8.95 \pm 0.10 \mu\text{m}$ ($p < 0.05$).

The effect of the chemical agents of the complex of monosodium glutamate, sodium nitrite and Ponceau 4R on week 8 led to significant increase of the mean values of the outer diameter by 8.77 %, compared to the values on week 4 of the experiment and by 44.17 % compared to the controls, accounting for $32.38 \pm 0.14 \mu\text{m}$ ($p < 0.05$). The diameter of the lumen increased insignificantly to $10.87 \pm 0.08 \mu\text{m}$; however, its values were by 61.04 % significantly greater compared to controls, accounting for $10.87 \pm 0.08 \mu\text{m}$. The height of epitheliocytes was also significantly greater both the values of the previous period of the experiment and the control values by 24.25 % and 35.61 %, respectively, accounting for $11.12 \pm 0.16 \mu\text{m}$ ($p < 0.05$).

On week 12 of consumption of complex of the food additives the outer diameter was $34.23 \pm 0.08 \mu\text{m}$, that was by 5.71 % and 52.40 % significantly greater compared to the values on week 8 of the experiment and values of the control group of animals, respectively ($p < 0.05$). The diameter of the lumen was by 4.97 % significantly lower compared to the values of the previous period of the experiment, accounting for $10.33 \pm 0.06 \mu\text{m}$ and by 53.03 % significantly greater compared to the controls ($p < 0.05$). The mean values of the height of epitheliocytes were by 5.22 % significantly greater compared to the values on week 8 of the experiment and by 42.68 % greater compared to the controls, accounting for $11.70 \pm 0.08 \mu\text{m}$ ($p < 0.05$).

The lumens of the glands in the neck were enlarged. The nuclei of exocrinocytes were located in the basal part. Dystrophic changes were noted in the cytoplasm. The number of mucocytes was progressively reduced. The number of poorly differentiated epitheliocytes was increased, in some cases single figures of mitosis were observed. The phenomena of desquamation of epitheliocytes in the lumens of the glands were detected (fig. 3b).

At the terminal stage of the experiment of consumption of the complex of monosodium glutamate, sodium nitrite and Ponceau 4R the mean values of the outer diameter were by 16.39 % significantly lower compared to the values of the previous period of the experiment, accounting for $28.62 \pm 0.15 \mu\text{m}$, though they were by 27.43 % significantly greater compared to the controls ($p < 0.05$). The diameter of the lumen of the glands was by 24.49 % significantly lower compared to the previous values of the experiment, accounting for $7.80 \pm 0.12 \mu\text{m}$, and by 15.56 % significantly greater compared to the controls ($p < 0.05$). The height of epitheliocytes was $11.47 \pm 0.18 \mu\text{m}$, that was by 1.97 % significantly lower compared to the previous values of the experiment, though it was by 39.88 % significantly greater compared to the values of the control group of animals ($p < 0.05$).

Thus, consumption of complex of the food additives at the early stages leads to a decrease in metric parameters in the area of the bottom of the fundic glands, with increasing height of epitheliocytes, and an increase in morphometric parameters in the body and neck of the glands, primarily due to direct exposure to chemical agents in the complex of food additives, which is identified with the action of various substances on mucous membranes [11]. Subsequently, the impact of food additives leads to spasm of the resistance and exchange sections of the hemomicrocirculatory bed [14] with the subsequent development of hypoxia and the development of inflammatory phenomena and edema. This reaction led to a decrease in morphometric parameters on week 4-8 of the experiment in the body and neck of the glands; however, in the area of the bottom of the glands the diameter was enlarged due to detachment of the basement membrane and the development of dystrophic lesions, manifested by the changes of the morphometric parameters of the height of epithelial cells. Due to the restorative-adaptive reactions aimed at neutralizing the alternative factor, no complete recovery occurred due to the constant negative effects of the complex of food additives, which by their strength outweighed the adaptive-protective capabilities of cellular components of the fundic glands and the development of dystrophic lesions.

Conclusion

The consumption of complex of the food additives of sodium nitrite, monosodium glutamate and Ponceau 4R results in the development of a complex reaction, which leads to changes in morphometric parameters of the fundic glands with the development of inflammatory reactions and edema. Restorative – adaptive reactions aimed at neutralizing the alternative factor and restoring the morphofunctional state of the glands of the stomach fundus do not lead to complete recovery of structural components due to the predominance of constant negative stimuli with dystrophic lesions, expressed by changes in morphometric parameters.

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