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V.P. Bilash, A.S. Grygorenko, G.A. Yeroshenko, K.V. Shevchenko, O.D. Lysachenko, I.M. Zviaholska, Yu.V. Tymoshenko, [1]T.V. Khilinska
Poltava State Medical University, Poltava, [1]Poltava V.G. Korolenko National Pedagogical University, Poltava

THE IMPACT OF THE COMPLEX FOOD ADDITIVES ON THE GLANDULAR APPARATUS OF THE RAT'S DUODENAL MUCOSA

e-mail: gala_umsa@ukr.net

The effect of a complex of food additives of monosodium glutamate, sodium nitrite and Ponceau 4R on the state of the crypt of the mucosa of the duodenum of rats in the early stages of the experiment leads to a decrease in mean morphometric values of crypt body components, which subsequently leads to disorders of microcirculation in blood vessels, the development of hypoxia and the occurrence of an inflammatory reaction. As a result, increasing dystrophic changes in the cells of the epithelium of the intestinal glands develop, which is manifested by a decrease in the average values of the quantitative indicator of the cellular composition of the epithelium of the crypts. Further, as a result of compensatory-restorative reactions, complete recovery does not occur, which is confirmed by a decrease in the mean values of the metric values of the crypt body with decreasing epithelial cell height, against a decrease in epithelial cell composition and local immunity during the experiment.

Key words: sodium glutamate, sodium nitrite, Ponceau 4R, duodenum, crypts, rats.

В.П. Білаш, А.С. Григоренко, Г.А. Єрошенко, К.В. Шевченко, О.Д. Лисаченко, І.М. Звягольська, Ю.В. Тимошенко, Т.В. Хілінська

ДІЯ КОМПЛЕКСУ ХАРЧОВИХ ДОБАВОК НА ЗАЛОЗИСТИЙ АППАРАТ СЛИЗОВОЇ ОБОЛОНКИ 12-ПАЛОЇ КИШКИ ЩУРІВ

Дія комплексу харчових добавок глутамату натрію, нітриту натрію та Понсо 4R на стан крипт слизової оболонки 12-палої кишки щурів на ранніх термінах експерименту призводить до зменшення середніх значень морфометричних показників компонентів тіла крипт, зі зменшенням висоти епітеліоцитів, відбувається внаслідок безпосереднього впливу складових елементів харчових добавок, що у подальшому призводить до порушень мікроциркуляції у судинах, розвитком гіпоксії та виникненням запальної реакції. Внаслідок чого розвиваються наростаючі дистрофічні зміни у клітинах епітелію кишкових залоз, що проявляється зменшення середніх значень кількісного показника клітинного складу епітелію крипт. Далі у результаті компенсаторно-відновлювальних реакцій повного відновлення не відбувається, що підтверджується зниженням середніх значень метричних показників тіла крипт зі зменшенням висоти епітеліоцитів, на тлі зниження чисельності клітинного складу епітелію і з напруженням місцевого імунітету протягом експерименту.

Ключові слова: глутамат натрію, нітрит натрію, Понсо 4R, 12-пала кишка, крипти, щурі.

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Currently, the study of the content of food additives in food and the analysis of its impact on human health is relevant, as manufacturers, using low-grade raw material, add them to their products, hiding behind the poor quality and stale of products [3]. Numerous experimental studies highlight the key role of food additives in the exacerbation of inflammatory bowel diseases; however, epidemiological studies of food additives at risk of inflammatory bowel disease are still limited [9]. The analysis of the content of food additives in domestic and foreign products has established that the most common additives used in the food industry are monosodium glutamate, sodium nitrite and Ponceau-4R. Flavor enhancer monosodium glutamate (E-621) stimulates and enhances taste sensations by increasing the sensitivity of the taste buds of the tongue. Long-term daily consumption of monosodium glutamate, even in safe doses, leads to morphological changes in the colonic wall in the form of focal inflammatory changes of the mucous membrane, circulatory disorders in the intestinal wall, as well as dysplastic changes, which can be harmful in terms of potentiating of carcinogenesis in the colonic mucosa [2, 6].

E-250 (sodium nitrite) food additive is widely used as a color retainer in manufacturing of meat products and a preservative to give products certain properties and maintain quality. Sodium nitrite is reported to have harmful toxic effects on multiple organs [5, 7].

Dyes used in the food industry are very popular for its property to give the product pleasant appearance, which is the initial stage of consumer attraction. One of such dye is the food additive E-124 (Ponceau-4R). The toxicity of azo dye ingredients, which are often used in food production, increases with increasing benzene rings in their structure [8, 14].

Thus, current scientific publications, elucidating the effects of various food additives on organs and systems, do not reveal the full picture of their impact, as the studies of their effects and properties are considered separately, whilst in practice they are often used in combination, therefore, the study of the changes, emerged during consumption of complex food additives is rational to date and is scientifically-substantiated and relevant research.

The purpose of the study was the establishment of the dynamics of changes in the metric values of the structural parameters of the crypts of the normal rat duodenal mucosa and the combined impact of monosodium glutamate, sodium nitrite and Ponceau-4R food additives.

Material and Methods. 84 outbred mature male rats were involved into the study. The rats of control group consumed drinking water and received saline per os. Sodium nitrite was administered at a dose of 0.6 mg/kg, monosodium glutamate at a dose of 20 mg/kg, 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. Prior animals' sacrifice, the evaluation of the rats' adaptive behavior was made with the use of the "open field" test [13].

The rats were sacrificed within 1, 4, 8, 12 and 16 weeks under thiopentone anesthesia overdose. Subsequently, the pieces of the duodenal wall, fixed in formalin, were embedded into paraffin [10]. Slices of the 5–10 μm thick were obtained in the sliding microtome. After staining with hematoxylin and eosin studied in the light microscope. The digital microscope equipped with DCM 900 digital microphoto attachment and software, adapted to the studies, have been used for microimaging and morphometric study. Quantitative counting of cellular representation of the intestinal glands was performed at the same magnification (1000×) in all time periods of the experiment. Statistical processing of morphometric data was performed using the *Exel* software [4].

Results of the study and their discussion. The morphometric study of the rat duodenal mucosa, namely the crypts, has found that the mean values of its depth accounted for 123.86±0.16 μm. The analysis of the crypt body showed the following results: the outer diameter of the crypts was 32.41±0.06 μm, the diameter of the lumen was 4.53±0.02 μm and the height of the epitheliocytes was 13.27±0.10 μm (table 1).

Table 1

Morphometric parameters of the crypts of the mucous membrane

Parameters	Depth	Crypt body (μm)		
	μm	D_o	D_l	H_e
Control	123.86±0.16	32.41±0.06	4.53±0.02	13.27±0.10
Week 1	158.59±0.31*	30.47±0.05*	3.55±0.03*	13.10±0.06*
Week 4	128.78±0.46*.**	25.45±0.15*.**	4.52±0.02*.**	11.06±0.03*.**
Week 8	115.56±0.20*.**	19.55±0.04*.**	4.04±0.03*.**	8.70±0.04*.**
Week 12	107.17±0.48*.**	24.54±0.04*.**	5.46±0.04*.**	8.59±0.04*.**
Week 16	118.35±0.22*.**	22.98±0.04*.**	4.00±0.03*.**	9.36±0.02*.**

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

The study of cellular representation has revealed the average number of exocrinocytes with the brush border (14.48 ± 0.29 FOV), undifferentiated enterocytes (2.50±0.05 FOV), goblet cells (10.11±0.23 FOV), and Paneth cells (3.50±0.05 FOV) (table 2).

Table 2

Quantitative composition of exocrinocytes in crypts

Parameter	Undifferentiated exocrinocytes (FOV)	Exocrinocytes (FOV)	Goblet cells (FOV)	Paneth cells	Intraepithelial lymphocytes (FOV)	The number of figures of mitosis (FOV)
Control	2.50±0.05	14.48±0.29	10.11±0.23	3.50±0.05	0.1±0.03	0.31±0.05
Week 1	2.50±0.15	15.98±0.10*	5.01±0.10*	3.00±0.10	0.2±0.04*	0.83±0.07
Week 4	3.63±0.05*.**	12.52±0.07*.**	5.34±0.08*.**	5.02±0.15*.**	1.84±0.08*.**	1.4±0.08*.**
Week 8	3.54±0.05*.**	13.54±0.08*.**	5.09±0.09*.**	3.09±0.08*.**	2.62±0.12*.**	1.51±0.09*.**
Week 12	2.51±0.07*.**	15.81±0.08*.**	5.56±0.12*.**	4.04±0.08*.**	2.81±0.10*	3.23±0.09*.**
Week 16	2.00±0.05*.**	13.00±0.05*.**	6.08±0.18*.**	6.00±0.05*.**	3.64±0.12*.**	2.31±0.09*.**

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

Invaginations or crypts (intestinal glands) were found in the mucous membrane of the duodenal wall at the basal surface of the villi, which were lined with columnar epitheliocytes with the brush border and prismatic undifferentiated enterocytes without brush border. Goblet exocrinocytes in the crypt were singly located among the columnar epitheliocytes, which by their structure were represented by typical mucosal cells, and had cyclicity associated with the accumulation and excretion of the secretory products

into the intestinal lumen. At the bottom of the crypt, exocrinocytes with acidophilic granularity – Paneth cells, which granules were stained with eosin, were located singly or in aggregations. Endocrinocytes were visualized in small amount. The lumen clearly visualized in the crypts. The lamina propria was represented by loose fibrous unformed connective tissue with its typical cellular composition and microvasculature (fig. 1).

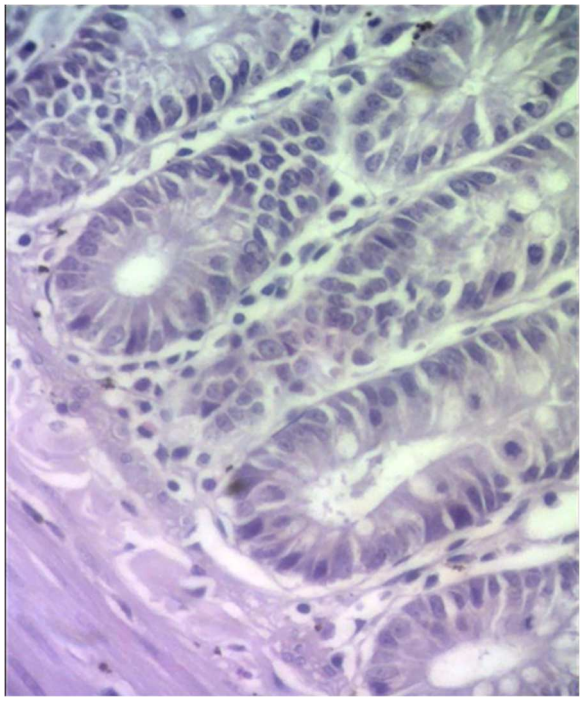

Fig. 1. Crypts (intestinal glands) of the duodenal mucosa of rats of control group. H&E stain. 10×ocular, 40×objective.

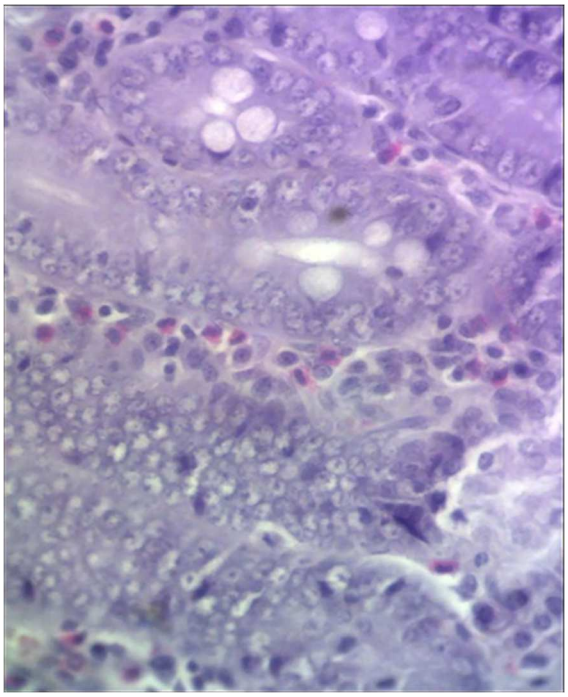

Fig. 2. Location and cellular composition of the crypts in the lamina propria of the duodenal mucosa on week 1 of consumption of complex food additives. H&E stain. 10×ocular lens, 40×objective.

On week 1 of consumption of complex food additives, an increase in the mean values of crypt depth by 28.04 % was noted, accounting for 158.59±0.31 μm ($p<0.05$). The outer diameter of the crypt body was significantly by 5.99 % lower than the values of the control group and accounted for 30.47±0.05 μm ($p<0.05$). Similarly, the diameter of the lumen was by 21.63 % lower with the mean values of 3,55±0,03 μm, as well as the values of the height of the epitheliocytes, accounting for 13.10±0.06 μm, that was by 1.28 % lower than the value of the control group of animals ($p<0.05$) (table 1). The quantitative composition of the cellular representation of the intestinal glands also changed, namely: the number of exocrinocytes with the brush border increased by 10.36%, the average number of which was 15.98±0.10 FOV and the number of goblet cells decreased by 50.45 %, accounting for 5.01±0.10 FOV; the average number of Paneth cells was by 14.29 % lower than the value in the control group, accounting for 3.00±0.10 FOV ($p<0.05$). The number of undifferentiated enterocytes remained unchanged (table 2). Histological study has revealed that the crypts were elongated with narrowed lumen or its complete absence. The increase in the number of exocrinocytes with the brush border, which were more orbicular and conjoined densely, and a decrease in goblet cells were noted. A large number of macrophages, neutrophils and plasma cells were visualized in the lamina propria (fig. 2).

Consumption of complex of monosodium glutamate, sodium nitrite and Ponceau- 4R on week 4 of the experiment led to a decrease in crypt depth by 18.80 % compared to the previous time period of the experiment, accounting for 128.78±0.46 μm, and was by 3.97 % greater than the values of the control group ($p<0.05$). The outer diameter of the crypt body decreased by 16.46 % and 21.47 % compared to the values on week 1 of the experiment and to the values of the control group, respectively, accounting for 25.45±0.15 μm ($p<0.05$). The lumen diameter of the crypt body, on the contrary, increased by 27.32 % compared to the previous time period of the experiment, accounting for 4.52±0.02 μm and was insignificantly by 0.22 % lower than the value in the control group of rats ($p<0.05$). The mean height of epitheliocytes was 11.06±0.03 μm, which was by 15.57 % lower than the values on week 1 of the experiment, and by 19.97 % lower than in the control group ($p<0.05$) (table 1). The quantitative counting of the cellular composition of the intestinal glands on week 4 has revealed a decrease in the number of exocrinocytes with the brush border by 21.65% compared to the previous time period of the experiment, accounting for 12.52±0.07

FOV, and was significantly by 13.34 % lower than the amount in the control group (p<0,05). The mean values of the number of goblet cells were insignificantly by 6.59 % greater than the amount on week 1, but still remained significantly by 47.18 % lower than the values in the control group of rats and accounted for 5.34±0.08 FOV (p<0.05). Quantitative counting also showed an increase in the number of Paneth cells, accounting for 5.02±0.15 FOV, and was significantly by 67.33 % and 43.43 % greater, compared to the values of the previous time period of the experiment and to the values in the control group, respectively (p<0.05). On week 4, an increase in the number of undifferentiated enterocytes was established, the mean number of which was 3.63±0.05 FOV, which was significantly by 45.20% greater than the previous values (p<0.05) (table. 2).

The visual study of the mucous membrane at high magnification on week 4 of the experiment revealed accelerated phenomena of hyperhydration, as evidenced by the increase in the amount of amorphous component in the intercellular substance of the lamina propria. The lumen of the crypts dilated significantly, which led to the deformation of the cells. A small number of goblet cells were in a state of accumulation of secretory granules, the nuclei of enterocytes without the brush border showed strong basophilia, occupied a basal position, the cells showed polymorphism. The nuclei of exocrinocytes with the brush border were centric; the cells were elongated. Intraepithelial lymphocytes were found in the depth of the epithelial layer (fig. 3a), and the figures of mitosis, indicating the beginning of the recovery process in response to the irritating factor, were noted (fig. 3b).

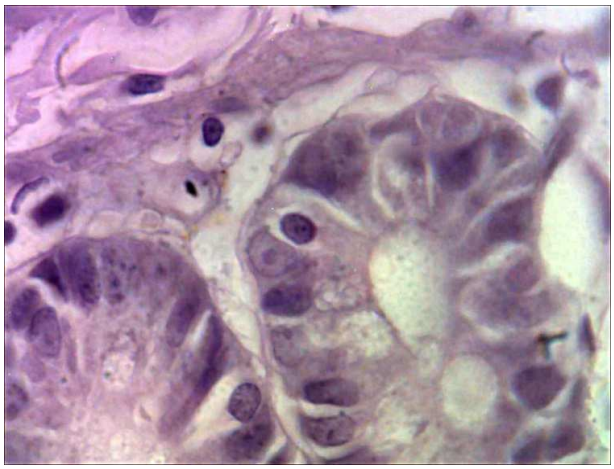

Fig. 3. Edema of the rat duodenal mucosa on week 4 of consumption of complex food additives. H&E stain. 10×ocular, 100× objective.

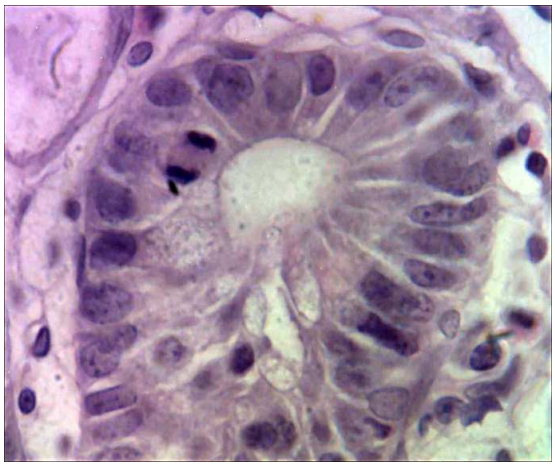

Рис. 3а. Mitosis in the epithelial cells of the crypts of rat duodenal mucosa on week 4 of consumption of complex food additives. H&E stain. 10×ocular, 100× objective.

Consumption of complex food additives on week 8 led to decrease in the depth of the crypts of the mucous membrane by 10.27 %, compared to the previous time period of the experiment, and accounted for 115.56±0.20 μm, which was also by 6.70 % lower than its values in the control group (p<0.05). The outer diameter of the body of the crypts responded by reduce in the mean values of morphometric parameters by 23.18 % compared to its values on week 4 of the experiment, and was 19.55±0.04 μm, which was significantly by 39.68 % lower than its value in the control group (p<0.05). The diameter of the lumen was significantly by 10.62 % and 10.82 % lower than the value of the previous time period of the experiment and the value of the control group, respectively, accounting for 4.04±0.03 μm (p<0.05). The value of the height of the epitheliocytes of the crypt body was significantly by 21.34 % and 34.44 % lower than the values of the previous time period of the experiment and the values of the control group, respectively, and on week 8 accounted for 8.70±0.04 μm (p<0.05). The number of exocrinocytes with the brush border increased by 8.15 %, compared to the previous time period of the experiment, and was 13.54±0.08 FOV; however, the above values were by 6.49 % lower compared to the control group (p<0.05). The mean number of goblet cells remained low, and accounted for 5.09±0.09 FOV, which was by 4.68 % lower than the values on week 8 of the experiment and significantly by 49.65 % lower than their number in control group of rats (p<0.05). The mean number of Paneth cells was significantly by 38.45% and 11.71% lower than the values of the previous time period of the experiment and their mean number in the control group, respectively, accounting for 3.09±0.08 FOV (p<0.05). The number of undifferentiated enterocytes accounted for 3.54±0.05 FOV, and was by 2.48 % greater than their values on week 8 of the experiment, which was significantly by 41.60 % greater than the values of controls (p<0.05).

Histological study of the specimens on week 8 of consumption of complex food additives of monosodium glutamate, sodium nitrite and Ponceau-4R revealed marked diminishing of the structural

elements of the crypts of the duodenal mucosa with the emergence of a large number of foci of desolation, epithelial cell deformation, narrowing of the lumen of crypt body with the phenomena of desquamation of the cryptic epithelium in the lumen of the intestinal glands (fig. 4a).

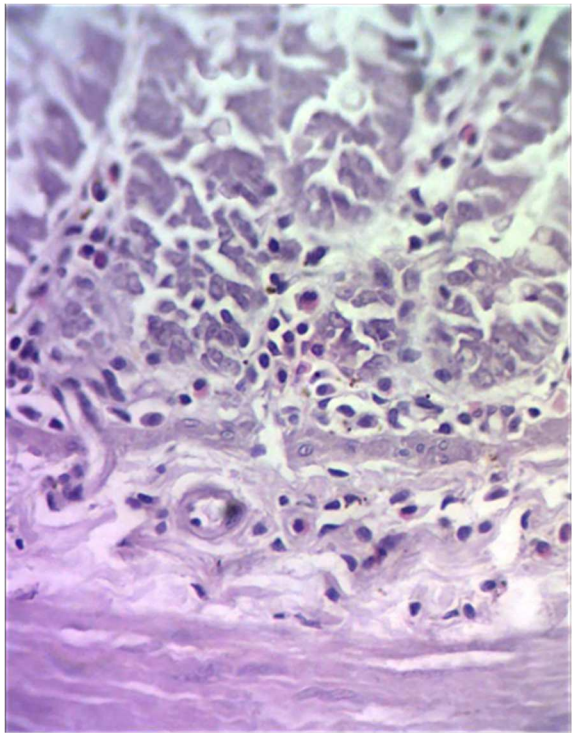

Fig. 4a. The phenomena of desquamation of the epitheliocytes of crypts of duodenal mucosa on week 8 of the experiment. H&E stain. 10×ocular, 100× objective.

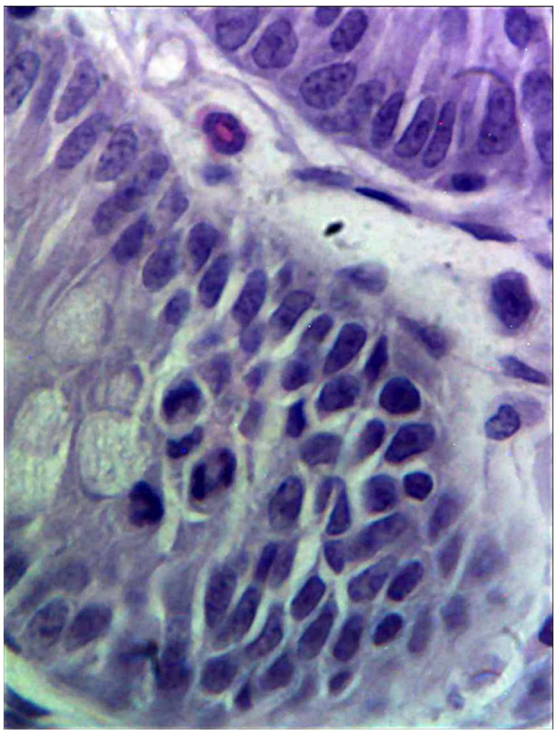

Fig. 4b. Mitosis in the cells of the cryptic epithelium of the duodenal mucosa on week 12 of the experiment. H&E stain. 10×ocular, 100× objective.

During the experiment, on week 12 of the consumption of complex food additives, the mean values of the crypt depth were 107.17±0.48 μm, which was by 7.26 % and 13.47 % lower than the values on week 8 and the values in the control group of animals, respectively ($p<0.05$). The outer diameter of the body of the crypts increased by 25.52 % compared to the previous values and accounted for 24.54±0.04 μm, which was by 24.28 % significantly lower than the values in the control group of rats ($p<0.05$). The diameter of the lumen was significantly by 35.15 % and 20.53 % greater than the value on the previous time period of the experiment and its value in the control group of rats, respectively, and on week 12 its values were 5.46±0.04 μm ($p<0.05$). The height of the epitheliocytes of the crypt body accounted for 8.59±0.04 μm, which was by 1.26% lower than on the previous time period of the experiment and by 35.27 % significantly lower than in the control group of animals ($p<0.05$). The study of the cellular composition of the crypts has established an increase in the number of exocrinocytes with the brush border that was by 16.77 % and 9.19 % greater than the values on week 8 of the experiment and the values in the control group, respectively, accounting for 15.81±0.08 FOV ($p<0.05$). The mean number of goblet cells increased by 9.23 % compared to the results of the previous time period, but progressively remained by 45.00% lower compared to the values of controls, accounting for 5.56±0.12 FOV ($p<0.05$). The number of Paneth cells increased by 30.74 % and 15.43 % compared to the results of the previous time period of the experiment and their values in the control group, respectively, accounting for 4.04±0.08 FOV on week 12 ($p<0.05$). The mean value of undifferentiated enterocytes decreased by 29.10% and accounted for 2.51±0.07 FOV, which was by 0.4% lower than the control values ($p<0.05$).

Histological study revealed intensification of the regenerative process in the crypts of the rat duodenal mucosa. A marked increase in the number of exocrinocytes with the brush border was visualized along with a decrease in undifferentiated enterocytes, involved in the process of mitosis and subsequent differentiation. Expansion of the gaps between the cells was noted. Goblet cells were few; they were in a state of accumulation of secretory granules (fig. 4b).

The depth of the crypts of the rat duodenal mucosa on week 16 of the experiment accounted for 118.35±0.22 μm, which was by 10.83 % significantly greater than the value on week 12, though it was by 4.45 % lower than the value of the control group ($p<0.05$). The outer diameter of the crypt body decreased compared to the previous time period of the experiment by 6.36%, accounting for 22.98±0.04 μm, that was by 29.10 % significantly lower than its value in the control group ($p<0.05$). The inner diameter of the crypt

body responded similarly to the impact of the complex of food additives by reducing its mean values by 26.74 % compared to the results of the previous time period of the experiment, and by 11.70 % compared to the results in the control group of animals and accounted for 4.00±0.03 μm ($p<0.05$). The values of the height of epitheliocytes at the end of the experiment increased by 8.96 % compared to the values on week 12, but remained significantly by 29.47% lower the values of the control group, accounting for 9.36±0.02 μm ($p<0.05$). The reduction of the linear dimensions of the structural components of the crypts led to a decrease in the quantitative parameters of cytological elements. Thus, the mean number of exocrinocytes with the brush border decreased by 17.77 %, compared to its number in the previous time period of the experiment, and was also by 10.22 % lower than the control values and accounted for 13.00±0.05 FOV ($p<0.05$). The long and complex process of differentiation of goblet cells on week 16 led to insignificant increase by 9.35 % in the number of mucosal cells compared to the parameters of the previous time period of the experiment, accounting for 6.08±0.18 FOV; however, these values still remained constantly lower by 39.86 % compared to the control group ($p<0.05$). The number of undifferentiated enterocytes also decreased, accounting for 2.00±0.05 FOV, and was significantly by 20.32 % and 20.00 % lower than the values of the previous time period of the experiment and the values of the control group, respectively ($p<0.05$). The mean number of Paneth cells, on the contrary, increased and was significantly by 48.51 % and 71.43 % greater than the values on week 12 and the control values, respectively, and accounted for 6.00±0.05 FOV ($p<0.05$) on week 16 of the experiment.

Thus, the impact of complex food additives of monosodium glutamate, sodium nitrite and Ponceau-4R at the beginning of the experiment leads to changes in morphometric parameters of the components of the crypt of the rat duodenal mucosa, which is manifested by a decrease in the outer diameter and diameter of the lumen of the intestinal glands along with a decrease in the height of epitheliocytes that first associated with the direct immediate effect of the compounds of the complex food additives on the mucous membrane. This response is caused by the changes in the state of the sections of the blood microcirculation, namely the decrease in the diameter of the lumen of both resistive, exchange and capacitive sections [1], and is confirmed by the data obtained in the previous studies on the state of the sections of microcirculatory bed, under the influence of the exogenous factors on the internal organs [10, 12]. Vessel constriction at the beginning of the experiment leads to imbalance in the lamina propria of the mucous membrane with the subsequent development of hypoxia, to which the cellular elements of loose fibrous unformed connective tissue respond, resulting in activated mast cells and leukocyte cells; the above phenomenon resulted in the emergence of the inflammatory reaction and edema, leading to an increase in the mean values of the crypt depth by 27.32% compared to the previous time period of the experiment, and an increase in the amount of amorphous component of intercellular substance led to compression and deformation of structural components of crypts and was confirmed by a decrease in morphometric values of the outer diameter by 15.57 %. The impact of the alternative factor led to general changes in the duodenal mucosa, triggering morphological mechanisms of acute inflammation in the form of dystrophic changes in the mucosa with subsequent atrophy of the duodenal wall, and was confirmed by a decrease in the quantitative parameters of the cells of the intestinal glands: decrease in the number of exocrinocytes with the brush border by 21.65 % and goblet cells by 6.59% on week 4 of the experiment. It is known that the impact of various pathogenic factors occurs when they, by their strength, outweigh the adaptive and protective capabilities of tissue and cellular components; therefore, the analysis of the average parameters of the morphometric study of structural components of crypts and quantitative parameters of cellular representation has established that during the second half of the experiment recovery processes occurred, which was confirmed by an increase in the number of undifferentiated enterocytes with their subsequent differentiation, indicating the increase in the number of mitotic figures in the epithelium of the crypts in the specimens. Apparently, the above process is complex and is characterized by different time periods of differentiation, which leads to disruption of parietal digestion, due to a decrease in the number of enterocytes with the brush border, which in the process of regeneration shifts to the villi, and protective properties of the mucosa due to progressive reduction of goblet cells; nevertheless, the number of Paneth cells compensatory increased by 71.43 %, which are known to synthesize dipeptidases and substances to enhance the protective properties of the mucous membrane. However, complete recovery did not occur, as evidenced by a decrease in the mean values of the morphometric study of crypt body parameters and a decrease in the average number of epithelial cells of the intestinal glands, which is primarily due to the constant impact of irritating exogenous factor [11], the emergence of imbalance between the sections of the microvasculature with disruption of the processes of blood perfusion through the vessels [1], the tension of local immunity and dystrophic changes in the rat duodenal mucosa.

Conclusion

It has been established that the effect of complex food additives of monosodium glutamate, sodium nitrite and Ponceau-4R on the state of the crypts of the rat duodenal mucosa at the early stages of the experiment caused a decrease in the mean values of the morphometric parameters along with a decrease in the height of epitheliocytes which led to microcirculation disorders in the microvasculature with the subsequent development of hypoxia and the occurrence of inflammatory reaction resulting in the development of accelerated dystrophic changes in the cells of the epithelium of the intestinal glands which led to a decrease in the mean values of the quantitative indicator of the cellular composition of the crypt epithelium. Subsequently, as a result of compensatory-restorative reactions in the second half of the experiment, partial restoration of morphometric parameters of the structural components of crypts and the amount of the cellular elements was noted; however, complete recovery did not occur, which was confirmed by a decrease in the mean values of the metric parameters of the crypt body along with a decrease in the height of epitheliocytes along with reduce in the amount of cellular composition of the epithelium and with the tension of local immunity during the experiment. Therefore, in response to the impact of chemicals that are components of the complex food additives, the mucous membrane responds with a constant inflammatory reaction with the subsequent development of dystrophy and damage, and destruction of epithelial cells.

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