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K.V. Shevchenko, G.A. Yeroshenko, I.M. Donets, A.S. Grygorenko, O.V. Klepets, V.M. Sokolenko, N.M. Sharlay
Poltava State Medical University, Poltava

RESTRUCTURING OF THE LUNG ALVEOLAR APPARATUS UNDER THE IMPACT OF THE COMPLEX OF FOOD ADDITIVES

e-mail: gala_umsa@ukr.net

The work presents the results of a morphometric and morphological study of the respiratory department of the lungs of rats under the complex action of food additives. It was established that the use of a complex of food additives sodium glutamate, sodium nitrite and Ponceau-4R leads to changes in the morphometric parameters of the alveolar apparatus of the rats' lungs and to violations of the structural organization of the components of the respiratory department of the lungs, which are characterized by dystrophic-destructive changes in type I and II alveolocytes, an increase the number of alveolar macrophages, accompanied by the development of interstitial and alveolar edema with the subsequent development of an allergic reaction. Restoration of morphometric indicators due to compensatory-restorative reactions does not occur.

Key words: food additives, sodium glutamate, sodium nitrite, Ponceau-4R, pulmonary alveoli, macrophages, neutrophils, eosinophils, lungs, rats.

К.В. Шевченко, Г.А. Єрошенко, І.М. Донець, А.С. Григоренко, О.В. Клепець, В.М. Соколенко, Н.М. Шарлай

СТРУКТУРНА ПЕРЕБУДОВА АЛЬВЕОЛЯРНОГО АПАРАТУ ЛЕГЕНЬ ЩУРІВ ПІД ВПЛИВОМ КОМПЛЕКСУ ХАРЧОВИХ ДОБАВОК

У роботі представлені результати морфометричного та морфологічного дослідження респіраторного відділу легень щурів при комплексній дії харчових добавок. Встановлено, що вживання комплексу харчових добавок глутамату натрію, нітриту натрію та Понсо-4R призводить до змін морфометричних показників альвеолярного апарату легень щурів та до порушень структурної організації компонентів респіраторного відділу легень, які характеризуються дистрофічно-деструктивними змінами в альвеолоцитах I та II типів, збільшенням кількості альвеолярних макрофагів, що супроводжуються розвитком інтерстиційного і альвеолярного набряків з послідуючим розвитком алергічної реакції. Відновлення морфометричних показників внаслідок компесаторно-відновлювальних реакцій не відбувається.

Ключові слова: харчові добавки, глутамат натрію, нітрит натрію, Понсо-4R, легеневі альвеоли, макрофаги, нейтрофіли, еозинофіли, легені, щури.

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

Currently, the distinguished feature of the up-to-date food technologies is the use of food additives, considered a group of substances of natural or artificial origin, used to improve the technology of manufacturing the products with characteristic organoleptic indicators and corresponding properties.

The use of food additives causes significant controversy both in the scientific community and the public, mainly due to the lack of thorough investigations on their effects on the human body, especially under the combined effect. The studies conducted do not provide a final conclusion regarding the varying degree of human susceptibility to the effects that occur under the combined action of food additives [1], and no data on their combined effect has been found.

According to our analysis of the content of food additives in the domestic and foreign products, the most common are monosodium glutamate, sodium nitrite and Ponceau 4R.

A review of the potential health hazards of monosodium glutamate was made by the international group of scientists. Although monosodium glutamate is generally considered safe by the food safety regulatory bodies, several studies question its long-term safety. Preclinical studies have linked the consumption of monosodium glutamate to cardiotoxicity, hepatotoxicity, neurotoxicity, low-grade inflammation, metabolic disorder, pretumor alterations and behavioral changes. Moreover, the association between the consumption of monosodium glutamate and tumorigenesis, increased oxidative stress and apoptosis in thymocytes, and genotoxic effects in lymphocytes have been reported. Clinical trials have focused primarily on the effect of monosodium glutamate on food intake and energy expenditure [15]. Sodium nitrite is an inorganic compound with the chemical formula $NaNO_2$. It is a white to slightly yellowish crystalline powder solid substance, odorless, high water soluble and hygroscopic. It is widely used in the industry and is a precursor to various organic compounds. Sodium nitrite is also used as a food

preservative and in the manufacturing of meat products. In humans, sodium nitrite causes smooth muscle relaxation, methemoglobinemia, and cyanosis [5, 12].

In the food industry, food colorants are widely used to give products the intended color or shade. Most of the colorants are water-soluble, odorless and give a permanent color to the food product, that is, they bind to it, which creates new allergenic complexes. In addition, food colorants are used to color the shells of medicinal forms (tablets, dragee, capsules, etc.). Food colorants, entering the body as haptens and binding to such proteins as serum albumin and others, become full-fledged antigens to which antibodies are synthesized. Permissible sanitary and hygienic standards are usually exceeded, which increases their allergenicity [6]. It has been reported about various immunopathogenic effects of the food colorants. Its consumption as part of food products and medications induces hypersensitivity, which is regarded as a side effect of drugs or food intolerance [4]. Numerous allergic reactions to food additives in the form of urticaria and angioedema, rhinitis, bronchitis, bronchial asthma have been described [9].

It is known that two main systems, namely, the respiratory and circulatory, are involved in the functioning of the lungs, which are structurally connected by the interstitial stroma, which runs throughout the lung, conjoining its various parts. Connective tissue plays one of the leading roles in the lungs. It promotes the transmission of the movements of the air pump, which is characteristic of the respiratory organ, and is the support of two other systems necessary for the regulation of respiratory function: lymph and nervous connections, serves as a barrier between the portions of the lung, thus ensuring metabolic communication between different cells of the lung parenchyma, being the essential microenvironment for these cells. Elements of mechanical functioning, namely, collagen and elastic fibers, prevail in the lung stroma. During inflammation, in addition to decay processes, characterized by the breakdown of carbohydrates, fats, proteins, depolymerization of protein-polysaccharide complexes and the appearance of underoxidized metabolic products, synthesis processes also begin to intensify. In this process, fibroblasts, connective tissue cells, which have a high synthesis activity, and histiocytes, which perform a protective role, become important [8].

Experimental modeling of various diseases on animals is one of the main methods of studying the patterns of development of pathological processes that often occur in clinical practice. To make the objective comparative assessment of experimental data and their subsequent extrapolation to a human, it is important to know the major normal morphometric parameters of organs and tissues in normal conditions and various etiological states.

The purpose of the study was to establish the dynamics of changes in the metric parameters and structural elements of the alveolar apparatus of the rat lungs in normal conditions and under the combined effect of the food additives, namely, monosodium glutamate, sodium nitrite and Ponceau 4R.

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 University. All of the animal procedures were carried out under 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) adopted in accordance with the ethical principles of the First National Congress on Bioethics and the Declaration of Helsinki.

Monosodium glutamate E621 (Multichem, China), Sodium nitrite E250 (Uralchem, China), Ponceau 4R E124 (Multichem, China). Distilled water was the solvent for ponceau 4R. The concentrations of food additives: sodium nitrite 0.6 mg/kg, monosodium glutamate 20 mg/kg, Ponceau 4R 5 mg/kg in 0.5 ml aq. dest.

The rats of control group (n=14) consumed drinking water and were administered with saline orally. The rats of the experimental group, with access to water ad libitum, were administered with 0.6 mg/kg sodium nitrite, 20 mg/kg monosodium glutamate and 5 mg/kg Ponceau 4R in 0.5 ml of distilled water once daily orally. The animals were sacrificed within 1, 4, 8, 12 and 16 weeks under thiopentone anesthesia overdose. The “open field” test evaluated the rats’ adaptive behavior [13]. After animals’ euthanasia, the fragments of the lungs were fixed in 2.5 % glutaraldehyde solution and 10 % formalin solution. Subsequently, the pieces of the lungs were embedded into epon-812 and paraffin, using the conventional technique [10].

Sections of 5–10 μm thick and semi-thin sections were obtained using the ARM 3600 and UMTP-7 microtomes, respectively. After staining with hematoxylin and eosin, as well as methylene blue, the sections were studied under the light microscope. The digital microscope, equipped with the Levenhuk D740T digital microphoto attachment, and adapted software have been used for microphotography and morphometric study.

Statistical processing of morphometric data was performed using the *Excel* software, that analyzed using parametric Student’s t-test. Besides, $p<0.05$ was considered to be statistically significant [2, 7].

Results of the study and their discussion. The findings of the morphometric study of the pulmonary alveolar apparatus of the control rats have established that the mean values of the alveolar lumen diameter were 41.51±1.99 μm; the thickness of the alveolar wall was 6.01±0.41 μm; the diameter of the type II alveolar cells was 7.78±0.27 μm. The mean value of the thickness of the visceral pleura was 3.61±0.03 μm (Table 1).

Table 1

The components of the pulmonary alveolar apparatus (μm)

Parameters	Alveolar lumen diameter	Thickness of the alveolar wall	Diameter of the type II alveolar cells	Thickness of the visceral pleura
Control group	41.51±1.99	6.01±0.41	7.78±0.27	3.61±0.03
Week 1	30.07±1.29*	19.78±0.66*	9.39±0.23*	3.47±0.04*
Week 4	79.65±4.13*.**	11.54±0.42*.**	12,61±0.40*.**	3.48±0.04*
Week 8	74.64±0.25*.**	7.70±0.09*.**	9.92±0.11*.**	4.98±0.07*.**
Week12	71.98±0.35*.**	17.78±0.19*.**	7.98±0.12**	5.61±0.08*.**
Week 16	69.25±0.63*.**	17.37±0.41*	7.65±0.10**	2.56±0.06*.**

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

Microscopic examination of rat lung tissue revealed intraalveolar macrophages in an average number of 0.3±0.03 (Table 2).

Table 2

Quantitative composition of leukocytes of lung alveoli (FOV)

Parameters	Number of intraalveolar macrophages	Number of segmented neutrophils	Number of eosinophils
Control group	0.3±0.03	0	0
Week 1	0.8±0.05*	0.1±0.01*	0
Week 4	2.9±0.08*.**	0.6±0.02	0
Week 8	2.55±0.09**	0	47.66±0.60*.**
Week 12	1.12±0.02*.**	0	36.02±0.59*.**
Week 16	0.98±0.01*	0	26.02±0.45*.**

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

Histological examination of the respiratory part of the lungs of control group of rats was established that the alveoli were almost cylindrical or polygonal in shape, lined with alveolar cells of two types, and almost the entire area was covered by the squamous type I alveolar cells with rod-shaped nuclei. Type II alveolar cells were located between the type I alveolar cells, and were orbicular with a low-basophilic round centric nucleus. The cytoplasm showed oxyphilia. The interstitial tissue was represented by loose fibrous unformed connective tissue with a large number of microvessels, mainly capillaries. Among the cells, in addition to fibroblasts, macrophages were noted, the vast majority of which were localized in the interalveolar spaces together with scarce lymphocytes and plasma cells, though, intraalveolar macrophages were also detected. Collagen fibers were present in the intercellular substance (Fig. 1).

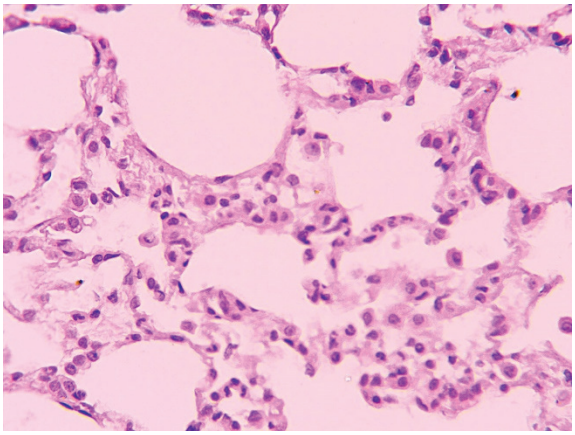

Fig. 1. Pulmonary alveolar apparatus of the rat of control group. H&E stain. Oc. lens: 10×magnification; ob. lens: 40× magnification.

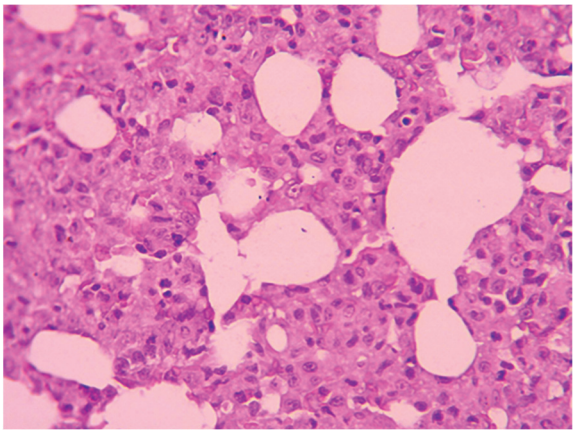

Fig. 2. Swelling of the interalveolar connective tissue with the phenomena of depletion of the exchange vessels on week 1 of consumption of the complex of food additives. H&E stain. Oc. lens: 10×magnification; ob. lens: 40× magnification.

Following one week of consumption of the complex of food additives, the mean values of the alveolar lumen diameter were by 27.56 % significantly lower and accounted for 30.07±1.29 μm (p<0.05). The thickness of the alveolar wall was by 229.12 % significantly greater, accounting for 19.78±0.66 μm

(p<0.05). The diameter of the type II alveolar cells was 9.39±0.23 μm, that was by 20.69 % significantly greater compared to the values of the control group of animals (p<0.05). On week 1, the mean values of the thickness of the visceral pleura were by 3.88 % significantly lower compared to its values of the control group (p<0.05). The findings of the microscopic study showed a decrease in the average amount of intraalveolar macrophages by 2.66 times (166.67 %), accounting for 0.8±0.05 FOV (p<0.05), and the appearance of segmented neutrophils in the amount of 0.1±0.01 FOV.

Histological study of the respiratory part of the lungs revealed a significant thickening of the interalveolar membranes along with narrowing of the lumen of the ovoid alveoli. Type I alveolar cells were more orbicular in shape, and the nuclei protruded into the lumen of the alveoli. Single type II alveolar cells were poorly defined and were polygonal in shape. In the interalveolar connective tissue, the number of the leucocytic cells increased. Among the vessels of the microcirculatory bed, the signs of both depletion (Fig. 2) and plethora were noted. Collagen fibers were not determined and (Fig. 3).

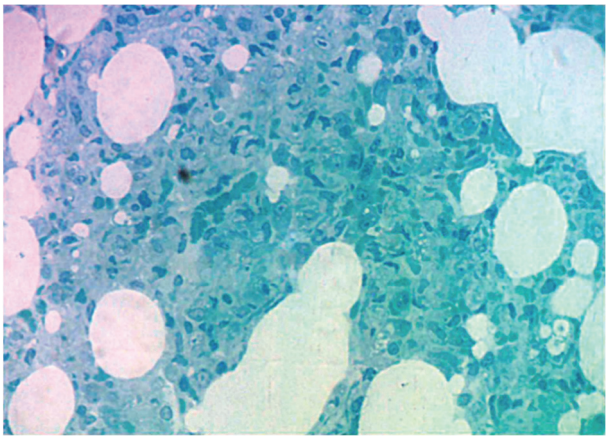

Fig. 3. Swelling of the interstitial connective tissue with the phenomena of plethora of the exchange vessels on week 1 of consumption of the complex of food additives. Methylene blue stain. Oc. lens: 10×magnification; ob. lens: 40× magnification.

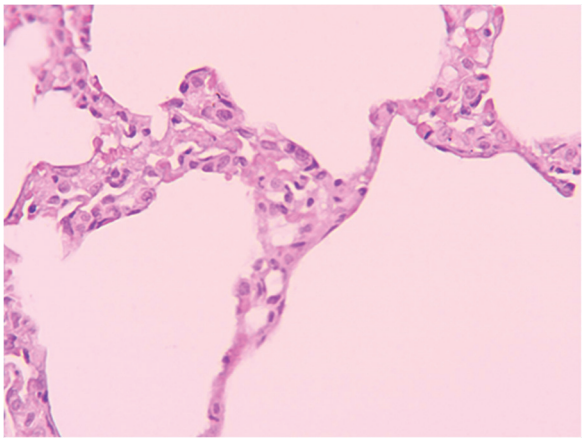

Fig. 4. The phenomena of desquamation of the alveolar cells and emphysematous dilatation of alveoli along with eosinophilic infiltration of the interalveolar interstitium on week 12 of consumption of the complex of monosodium glutamate, sodium nitrite and Ponceau 4R. H&E stain. Oc. lens: 10×magnification; ob. lens: 40× magnification.

On week 4 of consumption of the complex of monosodium glutamate, sodium nitrite and Ponceau 4R, the mean values of the alveolar lumen diameter were 79.65±4.13 μm, that was by 164.88 % significantly greater compared to the values of the previous time period of the study, and was also by 91.88 % significantly greater than the values of control group of rats (p<0.05). The thickness of the alveolar wall was by 41.66 % significantly lower compared to the values of the previous time period of the experiment, accounting for 11.54±0.42 μm; however, the above values were by 92.01 % significantly greater than the values of controls (p<0.05). On week 4, type II alveolar cells responded by significant enlargement of the diameter to the impact of the complex of food additives, with the mean values of 12.61±0.40 μm, that was by 34.29 % and 64.27 % greater than the values on week 1 of the experiment and values of the control group, respectively (p<0.05). The parameters of the thickness of the visceral pleura were by 0.29 % insignificantly greater compared to the values of the previous time period of the experiment, though they were by 3.60 % lower than the values of the control group of rats (p<0.05). The findings of the microscopic study revealed an increase in the amount of the intraalveolar macrophages by 3.63 times (262.50 %), compared to their amount on week 1 of the experiment and by 9.67 times (866.66 %) greater than the amount in the control group, accounting for 2.9±0.08 FOV; the average number of segmented neutrophils was by 6 times greater (500 %), compared both to their amount on week 1 of the experiment and control group, accounting for 0.6±0.02 FOV (p<0.05).

On week 8 of the pollutants' impact on the rats' lungs, the mean values of the alveolar lumen diameter were by 6.29 % significantly lower compared to the values on week 4, accounting for 74.64±0.25 μm, though it was by 79.81 % significantly greater than the values in the control group (p<0.05). The thickness of the alveolar wall was also by 33.28 % significantly lower compared to the value of the previous time period of the experiment and was by 28.12 % significantly greater than the values of the control group, accounting for 7.70±0.09 μm (p<0.05). The diameter of the type II alveolar cells accounted for 9.92±0.11 μm, that was by 21.33 % significantly lower than the values on week 4 of the observation, though it was by 27.51 % greater than the values of controls (p<0.05). On week 8, the mean values of the thickness of the visceral pleura were by 43.10 % greater, accounting for 4.98±0.07 μm, and it also was by 37.95 % significantly greater than the values of controls (p<0.05). The average number of intraalveolar macrophages

was by 1.14 times lower (12.07 %) and accounted for 2.55±0.09 FOV; however, the above parameters were by 8.5 times (750 %) greater than the values of controls ($p<0,05$). The complex effect of the food additives led to increase in eosinophils with their mean value of 47.66±0.60 FOV ($p<0.05$).

On week 12, the complex effect of monosodium glutamate, sodium nitrite and Ponceau 4R led to narrowing of the alveolar lumen by 3.56 %, compared to the previous time period of the experiment, accounting for 71.98±0.35 μm, and it was by 73.40 % significantly greater than the values of controls ($p<0.05$). The mean values of the thickness of the alveolar wall were by 130.91 % and 195.84 % significantly greater compared to the values on week 8 of the observation and the values of the control group of animals, respectively, accounting for 17.78±0.19 μm ($p<0.05$). The values of the diameter of the type II alveolar cells accounted for 7.98±0.12 μm, that was by 19.56 % and 2.57 % significantly greater than the values of the previous time period of the experiment and values of controls, respectively ($p<0.05$). The thickness of the visceral pleura was by 12.65 % greater compared to the values of week 8, accounting for 5.61±0.08 μm, that was also by 55.40 % greater than the values of control group of rats ($p<0.05$). The mean number of intraalveolar macrophages was by 2.28 times lower (56.08 %) compared to the previous time period of the experiment and accounted for 1.12±0.02 FOV; however, it was by 3.73 (273.33 %) greater than the values of controls ($p<0.05$). The number of eosinophils decreased to 36.02±0.59 FOV, that was by 1.32 times lower than the value of the previous time period of the observation ($p<0.05$).

Histological study revealed areas of emphysematous dilated alveoli in the respiratory part of the lungs. Type I alveolar cells were flattened with elongated rod-shaped nuclei. In some places, signs of desquamation of the epithelial lining of the alveoli were found. In the interalveolar interstitial tissue, capillaries with the signs of depletion along with enlarged lumen of the vessels were noted. The interalveolar spaces were thickened (Fig. 4).

At the end of the experiment, the impact of the complex of food additives led to narrowing of the diameter of the alveolar lumen by 3.79 % compared to its value on week 12, accounting for 69.25±0.63 μm, though the above parameters were by 66.83 % significantly greater than the values in the control group of animals ($p<0.05$). The thickness of the alveolar wall was by 2.31 % lower compared to the previous time period of the experiment, accounting for 17.37±0.41 μm, that also was by 189.02 % greater than the values of controls ($p<0.05$). The mean values of the diameter of the type II alveolar cells were by 4.14 % and 1.67 % lower compared to the values of week 12 and values of control group of rats, respectively ($p<0.05$). The thickness of the visceral pleura responded by the lowering of the mean values, accounting for 2.56±0.06 μm on week 16, that was by 54.38 % and 29.09 % significantly lower compared to the values of the previous time period of the observation and values of control group, respectively ($p<0.05$). At the end of the experiment, the mean number of intraalveolar macrophages was 0.98±0.01 FOV, that was by 1.14 times (12.5 %) significantly lower than the values of the previous time period and by 3.27 times (226,67 %) greater than the values of controls ($p<0.05$). The number of eosinophils decreased by 1.38 times (27.76) compared to the values on week 12 and accounted for 26.02±0.45 ($p<0.05$).

Thus, histological study revealed that alveolar apparatus of rats' lungs was represented by the respiratory tracts and alveoli covered with alveolar cells of two types, that could be used for objective comparative assessment of experimental data and their subsequent extrapolation to humans. The complex effect of monosodium glutamate, sodium nitrite and Ponceau 4R at the early stages of the experiment led to changes in the morphometric parameters of the alveolar apparatus, which was manifested by a significant narrowing of the diameter of the alveolar lumen and a significant increase of the mean values of the thickness of alveolar wall. These changes are associated with the primary endogenous effect of the complex of food additives, which led to the phenomena of hypoxia in the interalveolar connective tissue with the subsequent development of interstitial edema, which was also accompanied by the thinning of the visceral pleura and is confirmed by the histological study and are in concordance with previously conducted experiments related to the impact of various etiological factors on the organs and tissues [10, 14]. At the early stages of the experiment, an increase in the number of intraalveolar macrophages and the appearance of segmented neutrophils was observed, indicating the development of signs of nonspecific inflammation. Several authors report an increase in the number of intraalveolar macrophages under the impact of endogenous factors that accumulate in the blood in various conditions [3], which can be considered as the primary reaction of the alveolar macrophages in response to lung tissue alteration and the appearance of endogenous factors in the alveolar space. During the experiment, the phagocytic activity of macrophages resulted in destructive changes of the components of the aerogematic barrier of the lungs, which in turn leads to the release of blood plasma, containing macromolecular compounds and cell fragments, from the lumen of microvessels into the interstitial tissue, and then into the lumen of the alveoli with the development of interstitial and intraalveolar edema, which is accompanied by a significant decrease in lung

elasticity and is confirmed by increased mean values of the diameter of the alveolar lumen during the experiment, and in turn, the filling of the alveoli with liquid leads to the destruction of surfactant and enlargement, due to increased secretion, of the diameter of type II alveolar cells as a result of surfactant deficiency. On week 8 of the experiment, an increase in the number of eosinophils indicates the development of allergic reaction [6] to the impact of the complex of food additives, apparently first of all to synthetic dye Ponceau 4R in the middle of the experiment, that is confirmed by the works of foreign researchers [11] and leads to the development of asthmatic status, as evidenced by the histological study of emphysematous dilatation of the alveoli with desquamation of the epithelial lining of the alveoli on week 12 of the experiment (Fig. 3). Compensatory and restorative reactions of the body, which are known to be aimed at eliminating the alterative factor, do not lead to the restoration of the morphometric parameters of the pulmonary alveolar apparatus.

Conclusion

Consumption of the complex of monosodium glutamate, sodium nitrite and Ponceau 4R food additives leads to changes in the morphometric parameters of the alveolar apparatus of the lungs of rats and to destructive changes of the components of the respiratory part of the lungs, which are characterized by dystrophic destructive changes in type I and type II alveolar cells, an increase in the number of alveolar macrophages, accompanied by the development of interstitial and intra-alveolar edema with the subsequent development of allergic reaction and asthmatic status with the development of emphysematous dilatation of the lungs. Compensatory and restorative reactions do not lead to restoration of morphometric parameters.

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