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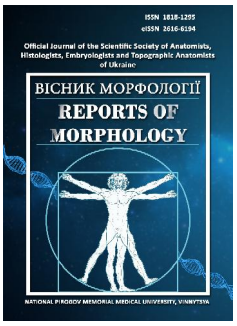

Morphometric characteristics of distal airways of guinea pigs sensitized with ovalbumin

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The reaction of the structural components of small bronchi and terminal bronchioles is the urgent issue of morphology and medicine in general, as well as one of the insufficiently studied issue in the study of morphological changes in the airways with allergic inflammation in the chronobiological aspect. The purpose of this work is to study the morphometric parameters of distal airways of guinea pigs sensitized with ovalbumin. We have studied the lung of 48 guinea pigs, using histological, morphometric and statistical methods under conditions of experimental ovalbumin-induced allergic inflammation, simulated by three times subcutaneous sensitization and subsequent 8-day intranasal inhalation of ovalbumin. The thickness of mucosa, muscular layer and adventitial layer was determined to assess morphometric parameters of bronchioles and terminal bronchioles. There are reactive changes in morphometric parameters of bronchioles on the 23rd and 30th days of observation, such as the thinning of mucosa and on the 36th day such as muscular-fibrous hyperplasia, accompanied by the narrowing of the bronchioles lumen. There are the most significant confirmed statistically changes in the terminal bronchioles on the 36th day of the experiment such as the thickening of mucosa and adventitial layer, accompanied by muscular hyperplasia and edema of the connective tissue stroma. Thus, sensitization and allergization with ovalbumin of experimental animals cause morpho-functional changes in the structural elements of the wall of bronchioles and terminal bronchioles, which have a staged, mainly multidirectional character and correspond to the main morphological manifestations of allergic inflammation with maximal changes in the late period of its development (the 36th day of the experiment).

Keywords: *airways, allergic inflammation, Ovalbumin, guinea pig.*

Introduction

There is a constant increase in the incidence of bronchial asthma (BA) in Ukraine and the world today, associated with environmental pollution, increased allergization of the population, deterioration of the gene pool of nations [7]. BA is considered today as a genetically determined disease with neuroendocrine and immune mechanisms of bronchial hypersensitivity development [4, 6, 10]. According to modern concepts, the development of bronchial hyperreactivity is the leading pathophysiological mechanism of the development of bronchial asthma, the degree of which correlates with the severity of the disease [8].

The morphological basis of bronchial hypersensitivity in bronchial asthma is allergic chronic inflammation of the airways, which is observed at all stages of the disease, regardless of its severity and course [11, 12]. Despite its importance, the problem of studying the morphogenesis of allergic inflammation of the distal airways often remains outside the field of vision of scientists. The number of works, devoted to the study of bronchial morphogenesis in various pathological conditions [9, 13], including allergic inflammation in the chronobiological aspect, is insignificant. Considering the above, the study of morphological changes in the distal airways with allergic inflammation in the chronobiological aspect is the urgent issue in experimental medicine.

The aim of this work is to study the morphometric parameters of the distal airways of guinea pigs sensitized with ovalbumin.

Materials and methods

This research is a part of the research work of Zaporizhzhya State Medical University "Immunomorphological

characteristics of internal organs under the influence of endo and exogenous factors on the body" state registration № 0118U004250.

The object of the experimental study was lung, removed from 48 sexually mature male guinea pigs weighing 450-600 g, which were kept in standard conditions of the vivarium of the Zaporizhzhya State Medical University. All manipulations were carried out in compliance with the basic principles of working with experimental animals in accordance with the provisions of the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Strasbourg, 1986), the General Ethical Principles for Animal Experiments adopted by the First National Congress on Bioethics (Kyiv, 2001), the Law of Ukraine "On the protection of animals from cruelty" (from 21.02.2006).

Allergic airway inflammation was induced by subcutaneous sensitization and followed challenging by intranasal inhalation with ovalbumin (OVA) (Sigma Aldrich, USA). Guinea pigs were actively sensitized by subcutaneous injections into the interscapular region of ovalbumin (0,5 mg/mL) with alum (10 mg/mL in saline) as an adjuvant (AlumVax Hydroxide vaccine adjuvant, OZ Biosciences France) on days 0, 7 and 14. From 21 to 28 days of the experiment, guinea pigs were challenged for 15 min with inhalation of either OVA (10 mg/mL in saline) via a nebulizer (Little Doctor International, Singapore, LD-211C) coupled to a plastic box. The animals were divided into 6 groups (8 animals in each group). The first four groups are animals sensitized and challenged OVA, withdrawn from the experiment, respectively, on the 23rd, 30th, 36th and 44th days after its start; 5 - control group, received injections and challenged with saline only; 6 - intact group. For the purpose of rational presentation of the obtained data and their interpretation, we conditionally distinguish the early (23rd, 30th days of the experiment) and late (36th and 44th days after the start of the experiment) periods of the development of allergic inflammatory process in lung.

The animals were withdrawn from the experiment by an overdose of thiopental anesthesia (50 mg/kg) according to the established terms (23rd, 30th, 36th and 44th days of the experiment). Histological sections were stained with hematoxylin-eosin. Masson staining was carried out to assess the organization of collagen fibers, alcian blue - to determine the dynamics of the distribution of glycosaminoglycans, the PAS reaction - to determine the dynamics of the distribution of glycoproteins.

The sections were viewed and photographed by a compound binocular light microscope (Primo Star, Zeiss, Germany). The thickness of mucosal layer, muscular layer and adventitial layer was determined to assess morphometric parameters of bronchioles and terminal bronchioles.

The research results were processed by modern statistical methods of analysis on a personal computer using the standard software package Microsoft Office 2010 (Microsoft Excel) and STATISTICA® for Windows 6.0 (StatSoft Inc., USA, license 46 No. AXXR712D833214FAN5). We use the Shapiro-Wilk test and the Kolmogorov-Smirnov test of consistency testing the hypothesis about the normal distribution of the studied parameters. We use the Kolmogorov-Smirnov homogeneity criterion testing the hypothesis that two independent samples belong to the same distribution law. The arithmetic means (M) and standard errors of the mean (±m) were calculated. The statistical significance of intergroup differences according to the data obtained was established using the parametric Student's t-test (p*) and the nonparametric U-Whitney-Mann test (p**). The obtained indicators were compared between the median and interquartile range Me (Q1; Q3). Differences between the compared values at the level of 95% ($p<0.05$) were considered statistically significant.

Results

There are the thickening of the wall of bronchioles and terminal bronchioles of guinea pigs sensitized with ovalbumins, showed by histological analysis. There are also changes in the structure of alveoli, the increase in the number of peribronchial and perivascular lymphoid nodules, compared to the control group (Fig. 1). The degree of the manifestation of inflammatory changes increases with the decrease of the diameter of bronchi, reaching its maximum in the terminal bronchioles. We also observe the bronchiolar epithelium desquamation into the airways lumen, partial exposure of the basement membrane, eosinophilic peribronchial infiltration (Fig. 1b).

Noteworthy is the uneven thickening of the muscular layer of bronchioles due to muscular hyperplasia (Fig. 1a, 1b). The lumen of some bronchioles is narrowed (Fig. 1d) or even obstructed (Fig. 1c), which is a morphological confirmation of bronchospasm in animals after OVA-sensitization and challenge. There are disorganization of fibrous elements, accumulation of PAS + positive material and numerous of mast cells in the connective tissue stroma by the adventitial layer of bronchioles (see Fig. 1c).

Morphological changes in the structural elements of bronchioles and terminal bronchioles, appeared at the light-optical level, have their own regular morphometric display.

There was no statistically significant difference between the indices of the thickness of the mucosal layer of bronchioles in animals of the intact and control groups ($p*/**>0.05$), which indicates that the experimental protocol does not itself affect the changes in the morphometric parameters of bronchioles. There is a tendency to the decrease in the thickness of the mucosal layer of bronchioles after OVA sensitization and challenge in the early period of development of experimental ovalbumin-induced allergic inflammation in lung. In animals of the first experimental group, the mucosal layer of bronchioles is 40.46±0.44 μm, which is 1.3 times less than that in the control group. The statistically significant thinning of the mucosal layer of bronchioles is also manifested on the

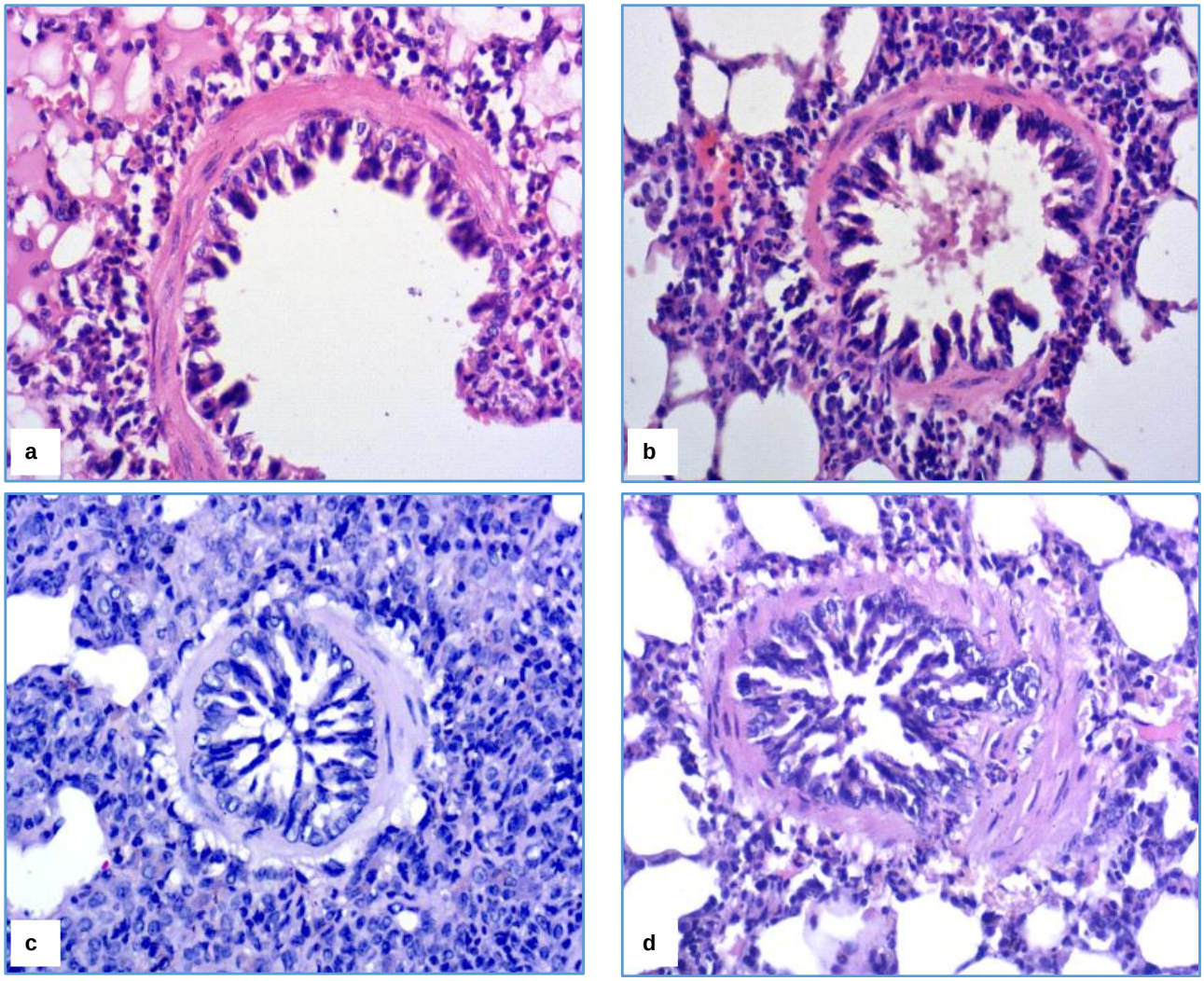

Fig. 1. Microscopic changes in the wall of bronchioles and terminal bronchioles of guinea pigs after OVA-sensitization and challenge on the 23rd (1a, 1b), 36th (1c), 44th (1d) days after the start of the experiment. 1a - muscular hyperplasia of the bronchiole; 1b - the bronchiolar epithelium desquamation, lymphocyte - leukocyte infiltration of the wall of the bronchiole; 1c - obstruction of the lumen of the bronchiole; 1d - the uneven thickening of muscular layer and narrowing of the lumen of the bronchiole. Stain: 1a, 1b - G. and E.; 1c - alcian blue; 1d - PAS reaction. x400.

30th day of the observation in animals of the second experimental group - 42.29±0.53 μm, which is 1.2 times less than the same indicator in the control group (Table 1).

There is a significant tendency towards the mucosal layer thinning of bronchioles in the late period of the development of allergic inflammation. A statistically significant decrease ($p^{**}<0.05$) in the mucosal layer thickness of bronchioles, compared to the control group, was observed in animals of the 3rd experimental group - 43.38±0.55 μm (see Table 1). There is a tendency for the indicator of the mucosal layer thickness in bronchioles riches those in the control group on the 44th day of observation.

There are no statistically significant differences between the muscular layer thickness of bronchioles of animals in the intact and control groups ($p^{*}/^{**}>0.05$). There is a tendency to the increase of the muscular layer thickness of bronchioles in the early period of the development of experimental ovalbumin-induced allergic inflammation in lung. A statistically significant thickening of the muscular layer of bronchioles is manifested from the 30th day of the experiment in animals of the 2nd experimental group - 25.59±0.23 μm, the increasing coefficient is 1.5 compared to the same indicator in the control group. In the late period of the development of allergic inflammation in guinea pigs' lung, a statistically significant muscular layer thickening by 1.7 times compared to the control appears in the third experimental group on the 36th day of observation - 29.1±0.46 μm (see Table 1). The tendency to the muscular layer thickening in bronchioles persists to the 44th day of the experiment in the fourth experimental group and is 24.73±0.12 μm, which is 1.5 times more than in the control group ($p^{*}/^{**}<0.05$).

The adventitial layer thickness in bronchioles is

Table 1. Morphometric indicators of the wall of bronchioles of guinea pigs sensitized with ovalbumin.

Group	I	II	III
1	40.46±0.44*/**	20.57±0.29	26.12±0.18*/**
2	42.29±0.53*/**	25.59±0.23*/**	29.68±0.31*/**
3	43.38±0.55**	29.1±0.46*/**	30.01±0.32*/**
4	48.63±0.49	24.73±0.12*/**	25.93±0.18*/**
5	52.04±0.66	17.0±0.28	22.19±0.25
6	53.74±0.49	17.17±0.35	22.26±0.28

Note: * - p<0.05 (Student's t-test); ** - p<0.05 (Whitney-Mann U-test) compared to the control group. M±m, (N=8); I - the mucosal layer thickness (μm); II - the muscular layer thickness (μm); III - the adventitial layer thickness (μm).

Table 2. Morphometric indicators of the wall of terminal bronchioles of guinea pigs sensitized with ovalbumin.

Group	I	II	III
1	21.23±0.2*/**	11.76±0.14	15.13±0.2
2	26.24±0.42	13.53±0.34**	14.02±0.09
3	32.17±0.39*/**	13.67±0.17*/**	18.76±0.1*/**
4	28.44±0.4	11.73±0.18	13.97±0.1
5	24.92±0.22	10.42±0.07	12.98±0.2
6	24.8±0.36	10.08±0.14	13.08±0.19

Note: * - p<0.05 (Student's t-test); ** - p<0.05 (Whitney-Mann U-test) compared to the control group. M±m. (N=8); I - the mucosal layer thickness (μm); II - the muscular layer thickness (μm); III - the adventitial layer thickness (μm).

22.26±0.28 μm in the intact group. There is no statistically significant difference between these parameters in animals of the intact and control groups. There is a tendency to the increase of the adventitial layer thickness in bronchioles during all periods of observation after OVA sensitization and challenge (see Table 1). In animals of the 1st experimental group, the thickness of the adventitial layer in bronchioles is 26.12±0.18 μm, which is 1.2 times more than in the control group. A statistically significant thickening of the adventitial layer in bronchioles, compared to the control group, is also present in the animals of the 2nd experimental group - 29.68±0.31 μm, which is 1.3 times more than in the control group. The maximal thickening of the adventitial layer in bronchioles of guinea pigs reaches in the late period of the development of allergic inflammation on the 36th day of observation - 30.01±0.32 μm, the increasing coefficient is 1.4, compared to the same indicator in the control group.

There was no statistically significant difference between the mucosal layer thickness in terminal bronchioles in animals of the intact and control groups (p*/**>0.05). After OVA sensitization and challenge in the early period of the development of allergic inflammation in the lungs, there is a tendency to the decrease in the mucosal layer thickness in terminal bronchioles. In animals of the 1st experimental group the mucosal layer thickness in terminal bronchioles is 21.23±0.2 μm, which is 1.2 times less than that of the control group (Table 2).

The gradual magnification in the thickness of the mucosal layer in terminal bronchioles is observed, starting from the 30th day of the experiment. A statistically significant thickening of the mucosal layer of terminal bronchioles appears on the 36th day of observation in animals of the 3rd experimental group - 32.17±0.39 μm, which is 1.3 times more than the same indicator in the control group.

There are no statistically significant differences between the parameters of the thickness of the muscular layer in terminal bronchioles in animals of the intact and control groups (p*/**>0.05). There is a tendency to the increase in the muscular layer thickness in terminal bronchioles in the early period of the development of experimental ovalbumin-induced allergic inflammation in lung of guinea pigs. A statistically significant thickening of the muscular layer in terminal bronchioles appears from the 30th day of the experiment in animals of the second experimental group - 13.53±0.34 μm, the increasing coefficient of 1.3 compared to the same indicator in the control group. In the late period of the development of allergic inflammation in the guinea pig lungs, a statistically significant thickening of the muscular layer of terminal bronchioles, compared to the control group, appears in the 3rd experimental group on the 36th day of observation - 13.67±0.17 μm (see Table 2). On the 44th day of observation, there is a tendency for the thickness of the muscular layer in terminal bronchioles approaches those in the control group.

In the intact group, the adventitial layer thickness in terminal bronchioles is 13.08±0.19 μm. There is no statistically significant difference between these parameters in animals of the intact and control groups. There is a tendency to the increase in the adventitial layer thickness of terminal bronchioles during all periods of observation after OVA sensitization and challenge (see Table 2). The statistically significant thickening of the adventitial layer in terminal bronchioles, compared to the control group, in animals of the 3rd experimental group is 18.76±0.1 μm, which is 1.5 times more than in the control group.

Discussion

Airways hyperresponsiveness develops as a result of bronchial allergic inflammation, caused by OVA sensitization and challenge [10]. The mechanism of inflammation is a cascade of processes involving neuroendocrine and immunocompetent cells, cytokines and mediators, the interaction of which forms the inflammatory process and the bronchial remodeling caused by it [14, 15].

Thus, this study determines the regularity of the dynamics of the structural elements of the wall of bronchioles and terminal bronchioles. The most significant and reactive changes in morphometric parameters of the wall of bronchioles were established on the 23rd and 30th days of observation - the thinning of the mucosal layer and on the 36th day - the thickening of the muscular layer and

the adventitial layer. In our opinion, the fact of the thinning of the mucosal layer in bronchioles is associated with alterative phenomenon in the early period of the development of airways allergic inflammation, namely the epithelial destruction and desquamation. Muscular hypertrophy in bronchioles is the morphological confirmation of the development of bronchial hyperreactivity as a result of OVA sensitization and challenge, which is also confirmed by the narrowing of the bronchial lumen, probably due to bronchospasm. The increase in the thickness of the adventitial layer of bronchioles is a confirmation of the development of the inflammatory process in the connective tissue, and, as a consequence, the development of stromal edema and disorganization of fibrous elements in the connective tissue of the bronchial wall. A similar trend of morphological changes in the bronchioles is observed in the studies of other scientists [1, 2, 3, 16]. The most significant changes in the terminal bronchioles, confirmed statistically, found on the 36th day of the experiment in the form of thickening of the mucosal and adventitial layers, is a consequence of muscular hypertrophy and edema of the connective tissue stroma in terminal bronchioles. It should also be noted the multidirectional reaction of the mucosal layer in terminal bronchioles in the early and late periods of the development of allergic inflammation.

In the future, we aim to study ultramicroscopic changes of epithelial cells, basement membrane, connective tissue stroma of bronchioles and terminal bronchioles of guinea pigs with allergic inflammation.

Conclusions

1. It has been established that OVA sensitization and challenge of experimental animals cause morphological and functional changes in the structural elements of the wall of bronchioles and terminal bronchioles, which have the staged, mainly multidirectional character and correspond to the main morphological manifestations of allergic inflammation.

2. Confirmation of the development of hyperreactivity of bronchioles and terminal bronchioles in experimental animals is muscular hypertrophy and narrowing of their lumen, which are most pronounced in the late period of development of allergic ovalbumin-induced inflammation (36th day of the experiment).

References

[1] Adner, M., Canning, Brendan J., Meurs, H., Ford, W., Ramos Ramirez, P., … & Dahlen, S.-E. (2020). Back to the future: re-establishing guinea pig in vivo asthma models. *Clinical Science,* 134(11), 1219-1242. https://doi.org/10.1042/cs20200394

[2] Almohawes, Z. N., & Alruhaimi, H. S. (2019). Effect of Lavandula dentata extract on Ovalbumin-induced Asthma in Male Guinea Pigs. *Brazilian Journal of Biology,* 80(1), 87-96. https://doi.org/10.1590/1519-6984.191485

[3] Antwi, A. O., Obiri, D. D., & Osafo, N. (2017). Stigmasterol Modulates Allergic Airway Inflammation in Guinea Pig Model of Ovalbumin-Induced Asthma. *Mediators of Inflammation,* 2017(2953930), 1-11. https://doi.org/10.1155/2017/2953930

[4] Barrios, J., Kho, A. T., Aven, L., Mitchel, J. A., Park, J.-A., Randell, S. H. … Ai, X. (2019). Pulmonary Neuroendocrine Cells Secrete γ-Aminobutyric Acid to Induce Goblet Cell Hyperplasia in Primate Models. *American Journal of Respiratory Cell and Molecular Biology,* 60(6), 687-694. https://doi.org/10.1165/rcmb.2018-0179oc

[5] Cai, Z., Liu, J., Bian, H., & Cai, J. (2019). Albiflorin alleviates ovalbumin (OVA)-induced pulmonary inflammation in asthmatic mice. *American Journal of Translational Research,* 11(12), 7300-7309. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6943473/

[6] Ha, E. H., Choi, J.-P., Kwon, H.-S., Park, H. J., Lah, S. J., Moon, K.-A. … Cho, Y. S. (2019). Endothelial Sox17 promotes allergic airway inflammation. J*ournal of Allergy and Clinical Immunology,* 144(2), 561-573.e6. https://doi.org/10.1016/j.jaci.2019.02.034

[7] Hrebniak, M. P., & Fedorchenko, R. A. (2019). Influence of industrial atmospheric pollution on the development of pathology of respiratory organs. *Pathologia,* 16(1), 81-86. https://doi.org/10.14739/2310-1237.2019.1.166314

[8] Klymenko, V. A., Kozhyna, O. S., & Zemlianskyi, K. V. (2019). Prevalence of bronchial asthma symptomatic manifestation among children of Kharkiv. *World of Medicine and Biology,* 15(68), 60-61. https://doi.org/10.26724/2079-8334-2019-2-68-61-65

[9] Koptev, M. M., Vynnyk, N. I., Kokovska, O. V., Filenko, B. M., & Bilash, S. M. (2018). The use of semi-thin section method in the study of stress-induced structural changes in lungs. *World of Medicine and Biology,* 14(64), 153. https://doi.org/10.26724/2079-8334-2018-2-64-153-156

[10] Lambrecht, B. N., & Hammad, H. (2014). The immunology of asthma. *Nature Immunology,* 16(1), 45-56. https://doi.org/10.1038/ni.3049

[11] Li, S., Koziol-White, C., Jude, J., Jiang, M., Zhao, H., Cao, G. … Morrisey, E. E. (2016). Epithelium-generated neuropeptide Y induces smooth muscle contraction to promote airway hyperresponsiveness. *Journal of Clinical Investigation,* 126(5), 1978-1982. https://doi.org/10.1172/jci81389

[12] Mitchel, J. A., Antoniak, S., Lee, J.-H., Kim, S.-H., McGill, M., Kasahara, D. I., … Park, J.-A. (2016). IL-13 Augments Compressive Stress-Induced Tissue Factor Expression in Human Airway Epithelial Cells. *American Journal of Respiratory Cell and Molecular Biology,* 54(4), 524-531. https://doi.org/10.1165/rcmb.2015-0252oc

[13] Nebesna, Z. M, & Yeroshenko, G. A. (2015). Histological and histochemical changes of the lungs after experimental thermal trauma. *World of Medicine and Biology,* 2(49), 141-145. https://womab.com.ua/ua/smb-2015-02-2/5084

[14] Nolin, J. D., Lai, Y., Ogden, H. L., Manicone, A. M., Murphy, R. C., An, D. … Hallstrand, T. S. (2017). Secreted PLA2 group X orchestrates innate and adaptive immune responses to inhaled allergen. *JCI Insight*, 2(21), 1-17. https://doi.org/10.1172/jci.insight.94929

[15] Popko, S. S., Evtushenko, V. M., & Syrtsov, V. K. (2020). Influence of pulmonary neuroendocrine cells on lung homeostasis. *Zaporozhye Medical Journal,* 22(4), 568-575. https://doi.org/10.14739/2310-1210.4.208411

[16] Zemmouri, H., Sekiou, O., Ammar, S., El Feki, A., Bouaziz, M., Messarah, M., & Boumendjel, A. (2017). Urtica dioica attenuates ovalbumin-induced inflammation and lipid peroxidation of lung tissues in rat asthma model. *Pharmaceutical Biology,* 55(1), 1561-1568. https://doi.org/10.1080/13880209.2017.1310905

МОРФОМЕТРИЧНА ХАРАКТЕРИСТИКА ДИСТАЛЬНИХ ВІДДІЛІВ ДИХАЛЬНИХ ШЛЯХІВ МОРСЬКИХ СВИНОК, СЕНСИБІЛІЗОВАНИХ ОВАЛЬБУМІНОМ

Попко С.С., Євтушенко В.М.

Актуальною проблемою морфології та медицини в цілому, а також одним із недостатньо досліджених явищ у вивченні морфологічних змін дихальних шляхів при алергічному запаленні в хронобіологічному аспекті залишається реакція структурних компонентів малих бронхів та термінальних бронхіол. Мета роботи - дослідити морфометричні параметри дистальних відділів дихальних шляхів морських свинок, сенсибілізованих овальбуміном. За допомогою гістологічного, морфометричного та статистичного методів вивчили легені 48 самців морської свинки в умовах експериментального овальбумін-індукованого алергічного запалення, яке моделювали шляхом триразової підшкірної сенсибілізації та наступної 8-денної інтраназальної інгаляції овальбуміном. Для дослідження морфометричних показників структурних елементів малих бронхів і термінальних бронхіол визначали товщину їх слизової, м'язової, та адвентиційної оболонок. Встановлено реактивні зміни метричних показників стінки малих бронхів на 23 і 30 доби спостереження у вигляді потоншення слизової оболонки та на 36 добу у вигляді потовщення м'язової пластинки слизової та адвентиційної оболонок, що супроводжувалися зменшенням просвіту бронхів. Найбільш значимі зміни у термінальних бронхіолах, підтверджені статистично, виявлені на 36 добу експерименту у вигляді потовщення слизової та адвентиційної оболонок, що є наслідком гіпертрофії гладеньких міоцитів і набряку сполучнотканинної строми термінальних бронхіол. Таким чином, сенсибілізація та алергізація овальбуміном експериментальних тварин викликають в структурних елементах стінки малих бронхів і термінальних бронхіол морфофункціональні зміни, котрі мають стадійний, переважно різнонаправлений характер і відповідають основним морфологічним проявам алергічного запалення з максимальними змінами протягом пізнього періоду розвитку (36 доба експерименту).

Ключові слова: *дихальні шляхи, алергічне запалення, овальбумін, морська свинка.*