EXPERIMENTAL RESEARCHES

INFLUENCE OF OBESITY ON THE TONE OF BRONCHIAL SMOOTH MUSCLES IN RATS

Birulina Ju.G.,
Ivanov V.V.,
Buyko E.E.,
Voronkova O.V.,
Hasanova R.R.,
Volkhina M.O.,
Nosarev A.V.,
Gusakova S.V.

Siberian State Medical University
(Moscovskii tract 2, Tomsk 634050,
Russian Federation)

Corresponding author:
Julia G. Birulina,
e-mail: birulina20@yandex.ru

ABSTRACT

Background. *Overweight and obesity are key factors for the occurrence of many morphofunctional disorders in organs and tissues, including bronchopulmonary system.*
The aim. *To study the influence of metabolic disorders that occur against the background of obesity on the state of the airways tone in rats.*
Materials and methods. *Obesity in male Wistar rats was induced using a high-fat and high-carbohydrate diet. In animals, body weight and fat mass were measured, and the heart-lung complex was extracted. In blood serum, the levels of glucose, insulin, leptin, triglycerides, and cholesterol were assessed. Bronchoalveolar lavage fluid was obtained by an open method, in which the concentration of protein, interleukin (IL) 6 and IL-10 was determined. The contractile activity of the isolated bronchial smooth muscle segments was studied using mechanographic method. The effect of acetylcholine (10^{-7}–10^{-4} M), indomethacin (10^{-5} M), and forskolin (10^{-7}–10^{-5} M) on the changes in the tone of airway smooth muscles was assessed.*
Results. *High-fat and high-carbohydrate diet caused an increase in body weight, visceral obesity, hyperglycemia, insulin resistance, leptinemia, dyslipidemia in rats of the experimental group. In the bronchoalveolar lavage fluid of experimental animals, an increase in the content of protein and IL-6 was found, which positively correlated with the level of leptin and the fat mass. In obese rats, the contractile responses of bronchial smooth muscle segments increased in response to the effect of the cholinergic agent acetylcholine. The bronchoconstrictor effect of acetylcholine was reduced by the cyclooxygenase inhibitor indomethacin. In turn, the adenylate cyclase activator forskolin caused relaxation of the airway segments smooth muscles in rats of both groups, which was more pronounced in the experimental group.*
Conclusion. *The obtained results indicate that the change in the reactivity of the respiratory tract can be the cause of bronchospastic conditions in obesity and of the inflammatory reaction in the respiratory system induced by obesity.*

Key words: *bronchi, smooth muscles, obesity, inflammation, insulin resistance*

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ВЛИЯНИЕ ОЖИРЕНИЯ НА ТОНУС ГЛАДКИХ МЫШЦ БРОНХОВ КРЫС

Бирулина Ю.Г.,
Иванов В.В.,
Буйко Е.Е.,
Воронкова О.В.,
Хасанова Р.Р.,
Вольхина М.О.,
Носарев А.В.,
Гусакова С.В.

ФГБОУ ВО «Сибирский государственный медицинский университет» Минздрава России (634050, г. Томск, Московский тракт, 2, Россия)

Автор, ответственный за переписку:
Бирулина Юлия Георгиевна,
e-mail: birulina20@yandex.ru

РЕЗЮМЕ

Обоснование. *Избыточная масса тела и ожирение являются ключевыми факторами для возникновения множества морфофункциональных нарушений в различных органах и тканях, в том числе в бронхолёгочной системе.*
Цель исследования. *Изучить влияние метаболических нарушений, возникающих на фоне ожирения, на состояние тонуса воздухоносных путей крыс.*
Материалы и методы. *Ожирение у крыс-самцов Wistar индуцировали с использованием высокожировой и высокоуглеводной диеты (ВЖВУД). У животных измеряли массу тела и жировой ткани, извлекали комплекс сердце-лёгкие. В сыворотке крови оценивали содержание глюкозы, инсулина, лептина, триглицеридов, холестерола. Открытым способом получали бронхоальвеолярную лаважную жидкость, в которой определяли концентрацию белка, интерлейкина (IL) 6 и IL-10. Сократительную активность изолированных гладкомышечных сегментов бронхов изучали механографическим методом. Оценивали влияние ацетилхолина (10^{-7}–10^{-4} М), индометацина (10^{-5} М), форсколина (10^{-7}–10^{-5} М) на изменение тонуса гладких мышц воздухоносных путей.*
Результаты. *ВЖВУД приводила к увеличению массы тела, висцеральному ожирению, гипергликемии, инсулинорезистентности, лептинемии, дислипидемии у крыс опытной группы. В бронхоальвеолярной лаважной жидкости экспериментальных животных обнаружено повышение содержания белка и IL-6, которое положительно коррелировало с уровнем лептина и массой жировой ткани. У крыс с ожирением происходило усиление сократительных ответов гладкомышечных сегментов бронхов в ответ на действие холиномиметика ацетилхолина. Бронхоконстрикторное действие ацетилхолина снижалось при воздействии ингибитора циклооксигеназы индометацина. В свою очередь, активатор аденилатциклазы форсколин вызывал расслабление гладких мышц сегментов воздухоносных путей крыс обеих групп, более выраженное в опытной группе.*
Заключение. *Полученные результаты свидетельствуют о том, что изменение реактивности дыхательных путей может являться причиной бронхоспастических состояний при ожирении и индуцируемой им воспалительной реакции в респираторной системе.*

Ключевые слова: *бронхи, гладкие мышцы, ожирение, воспаление, инсулинорезистентность*

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INTRODUCTION

Chronic non-communicable respiratory diseases represent an urgent medical and social problem due to high morbidity and early disability of patients [1, 2]. Overweight and diet-induced obesity are considered by researchers as risk factors for the development of bronchopulmonary pathology [3, 4]. Current evidence suggests a close relationship between chronic systemic inflammation induced by nutrients, metabolites, and bioactive substances of adipose tissue cellular elements and the development of increased airway reactivity [1, 5]. Several clinical studies have reported that patients with bronchial asthma and obesity have higher exacerbation rates, impaired response to corticosteroid treatment, and poor quality of life [6, 7].

The regulatory mechanisms underlying such abnormalities are a matter of debate, but have been shown to be directly related to dysfunction of contractile activity of smooth muscle cells of the airway wall [8, 9]. A recent study has demonstrated that airway smooth muscle cells in obesity are characterized not only by increased generation of contractions due to calcium-mediated mechanism, but also by a change in their bioenergetic profile accompanied by an increase in the rate of glycolysis [10]. Along with this, it has been noted that excessive adipose tissue accumulation and associated metabolic disorders can alter cellular composition and contribute to airway remodeling through various molecular mechanisms that form the basis of systemic inflammation [11, 12].

Since the pathological processes in the bronchopulmonary system is formed slowly, and clinical manifestations of respiratory failure are significantly delayed, it is difficult to study the pathogenesis of respiratory dysfunction in obese patients. Therefore, it is of particular interest to use biological models to evaluate the role of diet-induced obesity in the development and progression of the pathological process in the organs of the respiratory system [12, 13].

In this regard, the aim of the work was to study the influence of metabolic disorders that occur against the background of obesity on the state of the airways tone in rats.

MATERIALS AND METHODS

The experiment was performed on 18-week-old male Wistar rats (n = 18) that were on a high-fat and high-carbohydrate diet for 3 months [14]. Animals of the control group (n = 15) received standard laboratory diet during this period. When working with experimental animals, we adhered to the principles of humanity set forth in the European Community Directive (86/609/EEC) and the Declaration of Helsinki; the study was approved by the Ethics Committee of the Siberian State Medical University (protocol No. 8201 dated 27.03.2020).

At the end of the experiment, the animals were CO_2-euthanized. Blood was drawn from the heart, which was then centrifuged for 10 min at 2,000 g to obtain serum. Visceral adipose tissue, heart-lung complex were extracted. To determine the specific gravity of adipose tissue, samples were weighed on analytical balance (Pioneer PX224; OHAUS, PRC).

Bronchoalveolar lavage was performed by the open method on the isolated heart-lung complex [15]. Protein concentration in lavage fluid was determined spectrophotometrically (BCA Protein Assay Kit; Sigma-Aldrich, USA) and cytokines interleukin (IL) 6 and IL-10 by ELISA (Bender MedSystems GmbH kits, Austria). The concentration of glucose (Glucose-TR; Chronolab, Spain), triglycerides, cholesterol (Triglycerides, Cholesterol kits, respectively; Chronolab, Spain) was determined in serum by a colorimetric method, insulin (Insulin Rat ELISA Kit; Thermo Fisher Scientific, USA) and leptin (Rat Leptin ELISA Kit; ELK Biotechnology, PRC) – by ELISA. The HOMA-IR (Homeostasis Model Assessment of Insulin Resistance) index was calculated as serum insulin × serum glucose / 22.5.

The mechanical tension of isolated smooth muscle segments of rat airways (up to the 2nd order) was recorded using a mechanographic method (Myobath II; WPI, Germany). The resulting preparations were incubated in aerated chambers (95 % O_2, 5 % CO_2) filled with Krebs physiological solution (37 °C, pH = 7.35–7.40). Segment contracture was induced with potassium chloride (30 mM) or acetylcholine (10^{-5} M), the amplitude of contractile responses to which was taken as 100 %. The effects of acetylcholine (10^{-7}–10^{-4} M), indomethacin (10^{-5} M), and forskolin (10^{-7}–10^{-5} M) (all Sigma-Aldrich, USA) on contractile responses of airway segments were studied.

Data analysis of the study results was performed in SPSS Statistics 23 program (IBM Corp., USA). The obtained data are presented as mean (M) and standard deviation (± SD), median (Me) and 25th and 75th percentiles (Q_{25}; Q_{75}). Student's t-test or Mann – Whitney U test was used to analyze differences between samples. Differences were considered statistically significant at $p < 0.05$. The Spearman's Rank Correlation Coefficient was determined to assess the relationship between the indicators.

RESULTS

Animals administrated for 12 weeks on a special high-fat and high-carbohydrate diet had an increase in body weight, specific gravity of visceral adipose tissue. This high-fat and high-carbohydrate diet promoted the increase of glucose, insulin and leptin levels in the serum of rats belonging to the experimental group (Table 1). The value of insulin resistance index HOMA-IR in animals receiving high-fat and high-carbohydrate diets was statistically significantly higher than in the control group (Table 1). The rats of the experimental group also showed

TABLE 1

PHYSIOLOGICAL AND BIOCHEMICAL PARAMETERS IN RATS FROM CONTROL AND EXPERIMENTAL GROUPS (M ± SD)

Parameters	Control group (n = 15)	Experimental group (n = 18)
Body weight, g	433.3 ± 39.4	489.1 ± 47.9 (p = 0.01)
Specific gravity of visceral adipose tissue, g	2.2 ± 0.2	4.3 ± 0.6 (p < 0.001)
Fasting glucose, mM	4.7 ± 0.5	6.6 ± 0.4 (p < 0.001)
Insulin, pM	11.2 ± 0.8	24.2 ± 5.6 (p = 0.001)
HOMA-IR	0.4 ± 0.1	1.3 ± 0.4 (p = 0.004)
Leptin, ng/ml	3.1 ± 0.3	4.5 ± 0.1 (p = 0.01)
Cholesterol, mM	1.7 ± 0.2	2.3 ± 0.3 (p = 0.001)
Triglycerides, mM	0.7 ± 0.2	1.7 ± 0.5 (p = 0.001)

Note. p – statistically significant differences with the control group.

a statistically significant increase in the blood content of triglycerides and cholesterol compared to control animals (Table 1).

The study of bronchoalveolar lavage fluid revealed a 1.5-fold increase in protein concentration in rats of the experimental group compared to the control group (1.1 ± 0.3 g/l in the experimental group vs. 0.7 ± 0.2 g/l in the control group; p = 0.037). Also, a statistically significant increase in the concentration of IL-6 in lavage fluid (9.7 (9.4; 15.7) pg/ml in the experimental group vs. 5.3 (4.7; 9.2) pg/ml in the control group; p = 0.007) was found in animals of the experimental group, whereas the level of IL-10 did not differ between the investigated groups. There was a positive correlation between serum leptin levels and protein (r = 0.355; p = 0.020) and IL-6 (r = 0.573; p = 0.005) concentrations, as well as adipose tissue mass and IL-6 levels (r = 0.486; p = 0.005) in lavage fluid.

As a result of studying the constrictor reactions of airway smooth muscles, it was found that the action of the non-selective cholinergic receptor agonist acetylcholine (10^{-7}–10^{-4} M) caused a dose-dependent increase in the mechanical stress of bronchial segments of rats belonging to the control and experimental groups (Fig. 1). At the same time, the amplitude of contractile responses of ring segments in animals belonging to the experimental group was higher than in the control group in the concentration range from 5 × 10^{-6} to 5 × 10^{-4} M (p < 0.05). Airway segment pretreatment with the cyclooxygenase inhibitor indomethacin ((10^{-5} M) for 40 min caused a decrease in acetylcholine-induced contraction of segments in both control and experimental groups (Fig. 1). Statistically significant differences were found with the action of acetylcholine at concentrations of 5 × 10^{-6}–10^{-4} M (p < 0.05). The effect of indomethacin caused a greater inhibition of mechanical stress in the segments of the control group. Activation of adenylyl cyclase by addition of forskolin (10^{-7}–10^{-5} M) against the background of pre-contraction of bronchial segments with acetylcholine caused a dose-dependent decrease in the amplitude of the contractile response of segments obtained from animals of both study groups (Fig. 2). Moreover, a more pronounced drop in mechanical stress was observed in the segments of rats belonging to the experimental group.

DISCUSSION

Visceral obesity is a trigger for multiple metabolic disorders mediating neuroimmunoendocrine dysfunction at the systemic level [1, 3]. Current studies show that chronic inflammation associated with adipocyte hypertrophy and impaired secretory status is strongly associated with the development of airway hyperresponsiveness and may be a cause of respiratory pathology [3, 5, 9].

A key link in the pathogenesis of bronchopulmonary pathology is inflammation and remodeling of the airways, which are regulated by various cell types including immune, epithelial, smooth muscle and fibroblast cells. In obesity, immunocompetent cells of the airways

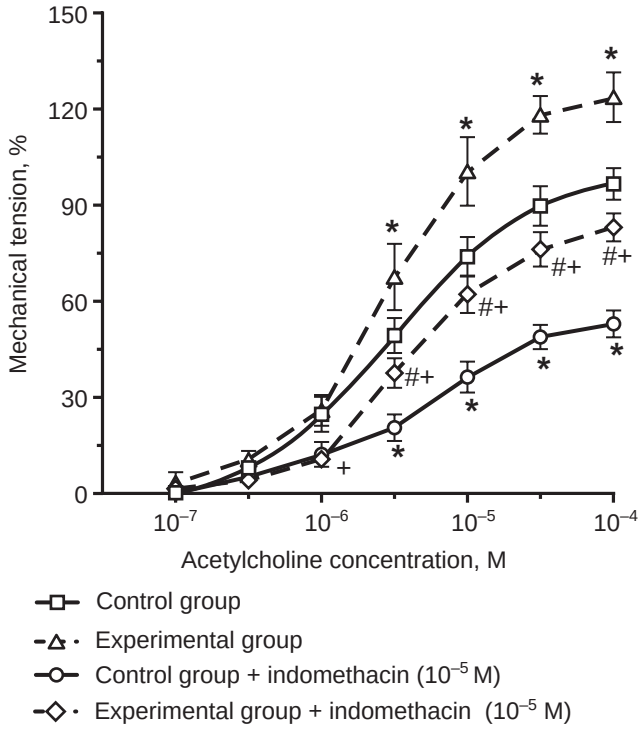

FIG. 1.

*The effect of acetylcholine on the contractile responses of bronchial smooth muscles in rats of control and experimental groups: * – statistically significant differences with the control group at p < 0.05; # – statistically significant differences with the control group + indomethacin (10^{-5} M) at p < 0.05; + – statistically significant differences with experimental group at p < 0,05*

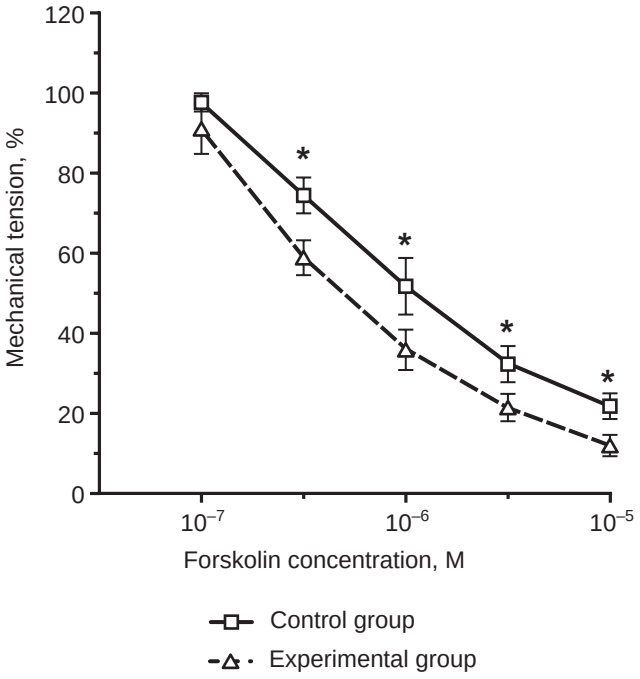

FIG. 2.

*The effect of forskolin on the contractile responses of bronchial smooth muscles in rats of control and experimental groups: * – statistically significant differences with the control group at p < 0,05*

can change their functional phenotype with a predominance of proinflammatory differentiation, which leads to hypersecretion of inflammatory cytokines, thickening of the bronchial wall, subepithelial fibrosis, neovascularization and increased proliferation and hypertrophy of smooth muscle cells [11, 12]. In the studies of A. Kurokawa et al. [8], K. Watanabe et al. [16] showed that the leptin is secreted almost exclusively by adipocytes, can enhance airway hyperresponsiveness by increasing the production of inflammatory mediators and accelerating the differentiation of myofibroblasts. Along with this, leptin increases the expression of intercellular adhesion molecules ICAM-1 in epithelial cells, which promotes the penetration of eosinophils and blood neutrophils into the airway mucosa [17], and various proinflammatory cytokines (IL-6, IL-8, IL-12, IL-12p40, IL-25, IL-33, CCL, etc.) produced by epithelial cells aggravate the inflammatory response of the airways and their hyperresponsiveness [11]. Activated epithelial cells can also enhance airway remodeling by promoting migration of airway smooth muscle cells into the epithelial layer [18]. Smooth muscle cells, in turn, can also maintain a pro-inflammatory status by secreting cytokines such as IL-1, IL-5, IL-6 and IL-8, TGF-β1 and VEGF [19]. The study of A. Matoba et al. [20] showed that an increase in the level of free long chain fatty acids (oleic and linoleic) through the MEK/ERK and PI3K/AKT signaling cascade induces proliferation and hyperplasia of smooth muscle cells of the airways *in vitro*.

To study the airway hyperresponsiveness development mechanisms and inflammation in obesity, the use of animal models is appropriate. We performed experiments on rats maintained for 12 weeks on a high-fat and high-carbohydrate diet. It was found that a high-fat and high-carbohydrate diet leads to changes in physiological and biochemical parameters, which are expressed in the development of diet-induced obesity, hyperglycemia, insulinemia, insulin resistance, leptinemia, dyslipidemia in animals of the experimental group. The obtained results correlate with the data of literature sources, which confirms the effectiveness of a high-fat and high-carbohydrate diet for modeling metabolic disorders, including those caused by increased accumulation of adipose tissue [8, 12]. Thus, biochemical and immunological analysis of bronchoalveolar lavage fluid of experimental animals showed active development of pathological process in the respiratory system. Rats of the experimental group showed an increase in protein and IL-6 concentration, which correlated with leptin levels and adipose tissue mass. In a similar study, mice treat-

ed with a high-fat diet showed increased levels of IL-5, IL-10, and tumor necrosis factor alpha in lavage fluid compared to those of control mice [21]. Thus, it can be concluded that obesity is accompanied by the development of inflammatory response in the bronchopulmonary system of experimental animals.

As it was noted earlier, the processes of airway remodeling are closely related to changes in the functional activity of respiratory epithelial cells and smooth muscles. The epithelium plays a significant role in regulating the contractile activity of airway smooth muscle by secreting various relaxant and constrictor factors, including NO, prostaglandin E_2, and EpDHF [13, 22]. The results of our study suggest that there is an increase in the contractile responses of bronchial smooth muscle cells in response to acetylcholine action during obesity. According to the literature, such cholinomimetic effects may be due to increased release of intracellular calcium from the sarcoplasmic reticulum and subsequent phosphorylation of myosin light chains [9] and/or overexpression of M-cholinergic receptors [23]. There is also evidence that bronchial hyperresponsiveness during obesity and diabetes is due to epithelial damage and impaired prostaglandin production [13, 24]. Pretreatment of airway segments with the cyclooxygenase inhibitor indomethacin leveled the acetylcholine-evoked contraction, but to a lesser extent in rats belonging to the experimental group. The decrease in mechanical tension of smooth muscles of segments against the background of indomethacin supports the hypothesis that it can have an inhibitory effect on phosphodiesterase [25] and thus increase the intracellular concentration of cyclic adenosine monophosphate. In turn, the effect of the adenylate cyclase activator forskolin caused dose-dependent relaxation of smooth muscles of airway segments in rats of both groups, more pronounced – in the experimental group. The obtained results indicate that the change in the reactivity of the respiratory tract can be the cause of bronchospastic conditions in obesity and of the inflammatory reaction in the respiratory system induced by obesity.

CONCLUSION

Overweight and obesity are key factors for a variety of morphofunctional abnormalities in various organs and tissues, including the bronchopulmonary system. This paper shows that high-fat and high-carbohydrate diet-induced obesity promotes the formation of a local inflammatory response and increased airway reactivity in experimental animals. Given the close relationship between obesity and bronchopulmonary dysfunction, an in-depth study of its pathogenesis is necessary in order to improve the methods of prevention and treatment of bronchial obstruction diseases in obese individuals.

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Conflict of interest

The authors of this article declare the absence of a conflict of interest.

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Information about the authors

Julia G. Birulina – Cand. Sc. (Biol.), Associate Professor at the Department of Biophysics and Functional Diagnostics, Siberian State Medical University, e-mail: birulina20@yandex.ru, https://orcid.org/0000-0003-1237-9786

Vladimir V. Ivanov – Cand. Sc. (Biol.), Head of the Center for Preclinical Research of the Central Research Laboratory, Siberian State Medical University, e-mail: ivanovvv1953@gmail.com, https://orcid.org/0000-0001-9348-4945

Evgeny E. Buyko – Junior Research Officer at the Central Research Laboratory, Siberian State Medical University, e-mail: buykoevgen@yandex.ru, https://orcid.org/0000-0002-6714-1938

Olga V. Voronkova – Dr. Sc. (Med.), Head of the Department of Biology and Genetics, Siberian State Medical University, e-mail: voronkova-ov@yandex.ru, https://orcid.org/0000-0001-9478-3429

Rezeda R. Hasanova – Cand. Sc. (Med.), Associate Professor at the Department of Biology and Genetics, Siberian State Medical University, e-mail: hasanova_rezeda@mail.ru, https://orcid.org/0000-0002-3250-7688

Mariya O. Volkhina – Student, Siberian State Medical University, e-mail: mashuta60@gmail.com, https://orcid.org/0000-0003-0783-7404

Alexey V. Nosarev – Dr. Sc. (Med.), Professor at the Department of Biophysics and Functional Diagnostics, Siberian State Medical University, e-mail: avnosarev@yandex.ru, https://orcid.org/0000-0002-0119-9707

Svetlana V. Gusakova – Dr. Sc. (Med.), Head of the Department of Biophysics and Functional Diagnostics, Siberian State Medical University, e-mail: gusacova@yandex.ru, https://orcid.org/0000-0001-5047-8668