FATTY ACIDS COMPOSITION OF BLOOD LEUCOCYTES MITOCHONDRIAL MEMBRANES IN MILD AND MODERATE ASTHMA

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RESUME

Relevance. *Systemic inflammation in bronchial asthma (BA) is associated with functional changes in subcellular structures, including mitochondria. Therefore, the study of mitochondrial structures is important for understanding the pathophysiological mechanisms of BA formation and progression. The functional activity of mitochondria largely depends on the qualitative and quantitative composition of fatty acids (FAs) of the mitochondrial membrane.*

Objective. *Establishing the characteristics of the FA composition of the mitochondrial membranes of blood leukocytes in patients with mild and moderate severity of bronchial asthma.*

Materials and methods. *The study involved 244 patients with BA (131 with mild and 113 with moderate severity) and 60 conditionally healthy individuals. The leukocyte suspension was obtained by Ficoll–Verografin density gradient centrifugation. Mitochondria were isolated from leukocytes by the standard method of differential centrifugation in sucrose medium. Methyl esters of FA were analyzed employing a gas chromatograph. Statistical processing of the results was performed using the STATISTICA 10.0 software package. The critical significance level (p) for testing statistical hypotheses was assumed at $p < 0.05$.*

Results. *With mild BA (of controlled and partially controlled course of disease) and with moderate BA of controlled course of disease, a compensatory increase in the summary indicators of monounsaturated fatty acids (MUFAs) and n-6 polyunsaturated fatty acids (PUFAs) occurs against the background of a decrease in the amount of saturated fatty acids (SFAs). With partially controlled BA of moderate severity, a breakdown in compensatory capabilities occurs, which is manifested in a decrease in the summary content of MUFAs and n-6 PUFAs. This may indicate both the development of pathological processes underlying BA and the activation of compensatory mechanisms at early stages of the disease.*

Conclusions. *Changes in the composition of fatty acids of mitochondrial membranes have been revealed in BA depending on the severity and level of disease control. Modification of the mitochondrial fatty acids composition may be an important criterion for assessing the progression of BA.*

Key words: *asthma, fatty acids, mitochondria, leukocytes, membranes*

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СОСТАВ ЖИРНЫХ КИСЛОТ МЕМБРАН МИТОХОНДРИЙ ЛЕЙКОЦИТОВ КРОВИ ПРИ БРОНХИАЛЬНОЙ АСТМЕ ЛЕГКОЙ И СРЕДНЕЙ СТЕПЕНИ ТЯЖЕСТИ

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РЕЗЮМЕ

Актуальность. *Системное воспаление при бронхиальной астме (БА) ассоциировано с функциональными изменениями субклеточных структур, в том числе митохондрий. Поэтому исследование митохондриальных структур является важным для понимания патофизиологических механизмов формирования и прогрессирования БА. Функциональная активность митохондрий во многом зависит от качественного и количественного состава жирных кислот (ЖК) митохондриальной мембраны.*

Цель. *Установление особенностей состава жирных кислот мембран митохондрий лейкоцитов крови при БА легкой и средней степени тяжести.*

Материалы и методы. *В исследование включены 244 больных БА (131 с легкой и 113 со средней степенью тяжести) и 60 условно здоровых лиц. Лейкоцитарную взвесь получали методом центрифугирования на градиенте плотности фиколл-верографин. Митохондрии из лейкоцитов выделяли стандартным методом дифференциального центрифугирования в сахарозной среде. Метиловые эфиры ЖК анализировали на газовом хроматографе. Статистическая обработка результатов производилась в программе «STATISTICA 10.0». Критический уровень значимости (p) при проверке статистических гипотез принимался при $p < 0,05$.*

Результаты. *При легкой БА (контролируемого и частично контролируемого течения) и при средней БА контролируемого течения на фоне снижения суммы насыщенных ЖК происходит компенсаторное возрастание суммарных показателей моноеновых (МЖК) и n-6 полиненасыщенных ЖК (ПНЖК). При частично контролируемой БА средней степени тяжести наблюдается срыв компенсаторных возможностей, что проявляется в снижении суммарного содержания МЖК и n-6 ПНЖК. Это может свидетельствовать как о развитии патологических процессов, лежащих в основе БА, так и об активации компенсаторных механизмов.*

Заключение. *При бронхиальной астме установлены изменения состава жирных кислот мембран митохондрий в зависимости от степени тяжести и уровня контроля заболевания. Модификация состава жирных кислот митохондрий может являться важным критерием для оценки прогрессирования БА.*

Ключевые слова: *бронхиальная астма, жирные кислоты, митохондрии, лейкоциты, мембраны*

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INTRODUCTION

The pathogenesis of bronchial asthma (BA) includes the processes of changing the energy state of cells and lipid metabolism, the development of oxidative stress and systemic inflammation [1]. The systemic inflammatory response in BA is associated with the damage processes of biomolecules formed in the conditions of oxidative stress and functional changes in subcellular structures, including mitochondria [2-5].

Previously, we have found that with mild and moderate BA, mitochondrial membrane potential (MMP) of immunocompetent cells decreases markedly depending on the severity and level of disease control [6]. Decreased mitochondrial membrane potential in asthmatic patients may correlate with altered mitochondrial membrane structure. This may be influenced by changes in both the qualitative and quantitative composition of mitochondrial membrane fatty acids (FAs). FAs play a key role in oxidative processes in mitochondria, not only meeting the cell's energy needs but also maintaining mitochondrial membrane homeostasis. These processes ensure the normal functioning of cellular structures [7-9]. Modifying the concentration and proportions of FAs adapts the membrane's lipid composition, which is aimed at maintaining optimal conditions for cellular functioning. FAs imbalance in mitochondrial membranes can lead to a reduction in their ability to maintain an electrochemical gradient, which contributes to the disruption of oxidative phosphorylation and adenosine triphosphate (ATP) production [8, 10]. Therefore, the study of mitochondrial structures is important for understanding the pathophysiological mechanisms of BA formation and progression.

OBJECTIVE

The objective of the present study is to establish the characteristics of the FA composition of the mitochondrial membranes of leukocytes in patients with mild and moderate BA.

MATERIALS AND METHODS

The *in vitro* study involved peripheral blood samples taken from 304 individuals. Among them, 60 individuals formed the control group (individuals without BA (27 males, 33 females)), 131 individuals were with mild BA (57 – controlled (28 males, 29 females), 74 – partially controlled (34 males, 40 females)), and 113 – with moderate BA (55 – controlled (29 males, 26 females), 58 – partially controlled (27 males, 31 females)). Average age was 42.5 ± 4.4 years. All individuals had normal body weight (body mass index was within the range of 18.5–24.99).

The diagnosis of BA was made in accordance with the (GINA) Global Strategy for Asthma Management and Prevention, and the International Classification of Diseases 10th Revision (ICD-10). The ACQ-5 (Asthma Control Questionnaire) test was used to determine the level of disease control. The ACQ scores ranged from 0.75 to 1.5 indicated partially controlled BA, while scores less than 0.75 indicated good control [11]. The study was conducted taking into account the requirements of the World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects, as amended in 2024, approved by the local Ethics Committee of the Vladivostok Branch of the Far Eastern Scientific Center of the Physiology and Pathology of Breath – Institute of Medical Climatology and Rehabilitation (Protocol No. 9 dated November 24, 2021). Voluntary informed consent was obtained from each patient for the health examination. Exclusion criteria from the study included the presence of acute infectious diseases in patients, as well as chronic diseases of internal organs in the acute phase, chronic heart failure in the decompensation stage, and uncontrolled BA.

Blood samples were taken in the morning in the fasted state. Peripheral blood was sampled into test glasses with anticoagulant (EDTA). The leukocyte suspension was isolated by centrifugation on a Ficoll–Verografin gradient (density of 1.077 g/ml).

Mitochondria were isolated from leukocytes by the standard differential centrifugation method in sucrose medium. The sucrose isolation medium was prepared using 0.75 M sucrose, 5×10^{-5} M ethylenediaminetetraacetic acid (EDTA), 0.5 % bovine serum albumin, and 0.01 M phosphate buffer. A pure supernatant with mitochondrial membranes was obtained by 5-fold centrifugation at 14.000 rpm (Z383K cooled centrifuge, Hermle LaborTechnik, Germany). Up to the analysis, the samples were stored at a temperature of –80°C. Lipids were extracted from mitochondrial membranes according to the Bligh and Dyer method (1959) using a chloroform mixture consisting of methanol (1:2 vol/vol) [12].

Methyl esters of FAs were obtained by sequential treatment of lipids according to the Carreau and Duback method (1978) [13], and then purified by preparative thin-layer chromatography in benzene. The methyl esters of FAs were eluted with chloroform; the solvent was evaporated using a vacuum rotary evaporator (IKA RV 05, Germany). Methyl esters of FAs were dissolved in 0.2 ml of hexane and analyzed on a GC-2010 gas chromatograph (Shimadzu, Japan) equipped with a flame ionization detector with a SH-Rtx-5MS capillary column (L = 30 m; d = 0.25 mm) in the following mode: input at 250°C (without flow separation), 160°C (2 min) – (2°C/min) – 260°C (10 min); summary chromatography time was 62 min, helium was used as a carrier gas, gas velocity in the column was 0.6 ml/min. The compounds were identified by comparing their mass spectra with the mass spectra of the NIST20 database. The data was presented as a percentage of the summary content of FAs.

The calculations were carried out employing STATISTICA software package version 10. The results of nonparametric descriptive statistics were presented in the form of median (Me), lower and upper quartiles (Q25; Q75).

The results of parametric statistics were presented as the arithmetic mean and the standard deviation sigma (M±σ). The Kruskal – Wallis-test was used for intergroup analysis of quantitative indicators in 3 or more groups, followed by post-hoc comparison using the Conover – Inman-test. The significance level of the differences was assumed at $p < 0.05$.

RESULTS

As a result of the study, the composition of FAs of mitochondrial membranes in BA was established (Table). Mitochondrial membranes are characterized by the presence of saturated, monounsaturated, and polyunsaturated FAs with a carbon skeleton length ranging from 10 to 24 carbon atoms. FAs that did not exceed 0.03 % are not included in the table.

Analysis of the quantitative composition of the FAs of mitochondrial membranes has revealed a decrease in the main pool of saturated fatty acids (SFAs) in patients with BA. Thus, in comparison with the control group, with mild BA, the content of myristic acid (14:0) has decreased by 30 % ($p < 0.001$) and 37 % ($p < 0.001$), while with moderate BA, it was lower by 63 % ($p < 0.001$) and 80 % ($p < 0.001$) for controlled and partially controlled course of disease, respectively. A decrease in stearic acid content (18:0) was observed as well: a decrease of 30 %

TABLE

COMPOSITION OF FAS OF MITOCHONDRIAL MEMBRANES IN BA

Groups	Indicators, %					Kruskal-Wallis-test	Conover-Inman-test
	Control group (1) *n*=60	Mild BA		Moderate severity BA			
		Controlled (2) *n*=57	Partially controlled (3) *n*=74	Controlled (4) *n*=55	Partially controlled (5) *n*=58		
Saturated fatty acids (SFAs)							
Myristic acid (14:0)	0.3 (0.26; 0.35)	0.21 (0.18; 0.23)	0.19 (0.14; 0.22)	0.11 (0.07; 0.13)	0.06 (0.04; 0.07)	H=41.4 p<0.001	p_{1-2}<0.001 p_{1-3}<0.001 p_{1-4}<0.001 p_{1-5}<0.001 p_{2-4}<0.001 p_{3-5}<0.001
Palmitic acid (16:0)	38.8 (38.69; 38.87)	38.03 (37.96; 38.09)	38.25 (38.18; 38.29)	38.64 (38.59; 38.66)	36.12 (36.06; 36.15)	H=11.6 p=0.036	p_{1-2}=0.140 p_{1-3}=0.213 p_{1-4}=0.146 p_{1-5}<0.032 p_{2-4}=0.094 p_{3-5}=0.023
Stearic acid (18:0)	49.07 (48.98; 49.12)	34.26 (34;19; 34;29)	38.85 (37;78; 39.9)	42.45 (42.4; 42.51)	44.12 (43.07; 44.88)	H=43.5 p<0.001	p_{1-2}<0.001 p_{1-3}<0.001 p_{1-4}<0.001 p_{1-5}<0.001 p_{2-4}<0.001 p_{3-5}<0.001
Arachidic acid (20:0)	0.91 (0.86; 0.97)	0.89 (0.82; 0.91)	0.84 (0.78; 0.87)	0.81 (0.78; 0.82)	0.76 (0.71; 0.79)	H=28.7 p=0.007	p_{1-2}<0.001 p_{1-3}<0.001 p_{1-4}=0.018 p_{1-5}=0.030 p_{2-4}<0.001 p_{3-5}<0.001
Behenic acid (22:0)	1.8 (1.76; 1.83)	1.72 (1.69; 1.75)	1.04 (1; 1.08)	0.54 (0.49; 0.58)	0.45 (0.41; 0.5)	H=36.2 p<0.001	p_{1-2}=0.045 p_{1-3}<0.001 p_{1-4}<0.001 p_{1-5}<0.001 p_{2-4}<0.001 p_{3-5}<0.001
Monounsaturated fatty acids (MUFAs)							
Oleic acid (18:1n-9)	1.58 (1.52; 1.62)	3.16 (3.09; 3.2)	4.56 (4.48; 4.61)	0.55 (0.51; 0.59)	1.02 (0.98; 1.05)	H=39.7 p<0.001	p_{1-2}<0.001 p_{1-3}<0.001 p_{1-4}<0.001 p_{1-5}<0.001 p_{2-4}<0.001 p_{3-5}=0.004

TABLE (*continued*)

Erucic acid (22:1n-9)	2.06 (1.96; 2.12)	10.52 (10.44; 10.6)	2.21 (2.17; 2.26)	11.66 (11.57; 11.71)	0.68 (0.61; 0.72)	H=36.5 p<0.001	p_{1-2}<0.001 p_{1-3}=0.007 p_{1-4}<0.001 p_{1-5}<0.001 p_{2-4}<0.001 p_{3-5}<0.001
Polyunsaturated fatty acids (PUFAs)							
Linoleic acid (18:2n-6)	1.06 (1.01; 1.12)	1.79 (1.69; 1.85)	7.27 (7.16; 7.34)	3.88 (3.82; 3.96)	0.47 (0.42; 0.49)	H=41.0 p<0.001	p_{1-2}<0.001 p_{1-3}<0.001 p_{1-4}<0.001 p_{1-5}=0.003 p_{2-4}<0.001 p_{3-5}<0.001
Eicosadienoic acid (20:2n-6)	0.11 (0.07; 0.17)	0.38 (0.3; 0.41)	0.16 (0.12; 0.19)	0.16 (0.14; 0.2)	0.04 (0.03; 0.06)	H=9.2 p=0.032	p_{1-2}<0.001 p_{1-3}=0.081 p_{1-4}=0.075 p_{1-5}=0.049 p_{2-4}=0.044 p_{3-5}=0.003
Arachidonic acid (20:4n-6)	0.91 (0.7; 0.95)	0.18 (0.17; 0.22)	0.17 (1.09; 0.18)	0.81 (0.75; 0.82)	0.71 (0.64; 0.77)	H=17.9 p=0.004	p_{1-2}<0.001 p_{1-3}<0.001 p_{1-4}=0.062 p_{1-5}=0.059 p_{2-4}<0.001 p_{3-5}<0.001
Summary FAs indicators							
Summary SFAs	90.88 (90.55; 91.14)	75.78 (75.52; 76.03)	79.51 (78.21; 80.71)	82.55 (82.33; 82.7)	81.51 (80.29; 82.39)	H=46.2 p<0.001	p_{1-2}<0.001 p_{1-3}<0.001 p_{1-4}<0.001 p_{1-5}<0.001 p_{2-4}<0.001 p_{3-5}<0.001
Summary MUFAs	3.64 (3.48; 3.74)	13.68 (13.53; 13.8)	6.77 (6.65; 6.87)	12.21 (12.08; 12.3)	1.7 (1.59; 1.77)	H=49.9 p<0.001	p_{1-2}<0.001 p_{1-3}<0.001 p_{1-4}<0.001 p_{1-5}<0.001 p_{2-4}<0.001 p_{3-5}<0.001
Summary PUFAs	2.08 (1.78; 2.24)	2.35 (2.16; 2.48)	7.6 (7.32; 7.71)	4.85 (4.71; 4.98)	1.22 (1.09; 1.32)	H=51.4 p<0.001	p_{1-2}<0.001 p_{1-3}<0.001 p_{1-4}<0.001 p_{1-5}<0.001 p_{2-4}<0.001 p_{3-5}<0.001
18:1n9/18:0, r.u.	0.03 (0.03; 0.04)	0.09 (0.08; 0.1)	0.12 (0.11; 0.13)	0.01 (0.01; 0.02)	0.02 (0.01; 0.03)	H=48.6 p<0.001	p_{1-2}<0.001 p_{1-3}<0.001 p_{1-4}<0.001 p_{1-5}<0.001 p_{2-4}<0.001 p_{3-5}<0.001

(p < 0.001) and 21 % (p < 0.001) was noted in mild BA, 14 % (p < 0.001) and 10 % (p < 0.001) in moderate BA in the controlled and partially controlled groups, respectively. The content of arachidic acid (20:0) has decreased by 2 % (p < 0.001) and 8 % (p < 0.001) with mild severity BA, by 11 % (p = 0.018) and 17 % (p = 0.030) with moderate severity respectively in controlled and partially controlled BA, respectively. A decrease in the level of behenic acid (22:0) by 4 % (p = 0.045) and by 42 % (p < 0.001) was observed in mild BA, while by 70 % (p < 0.001) and 75 % (p < 0.001) in moderate BA for controlled and partially controlled course of disease, respectively.

Against the background of a decrease in the proportion of SFAs, multidirectional changes in the relative content of monounsaturated fatty acids (MUFAs) in BA were revealed relative to the control group. The level of oleic acid (18:1n-9) has increased twice (p < 0.001) and 2.9-fold (p < 0.001) in mild BA and partially controlled BA, while in moderate BA it has decreased by 65 % (p < 0.001) and 35 % (p = 0.004) in controlled and partially controlled

BA, respectively. The relative content of erucic acid (22:1n-9) in the controlled course of disease increased 5.1-fold ($p < 0.001$) in mild BA, 5.7-fold ($p < 0.001$) – in moderate BA, and by 7 % ($p = 0.007$) – in partially controlled mild BA. At the same time, a decrease in the content of erucic acid (22:1n-9) by 67 % ($p < 0.001$) was observed in partially controlled BA of moderate severity.

A certain features in changing the content of linoleic acid (18:2n-6) should be noted in the pool of PUFAs. This change is characterized by an increase in the relative content of linoleic acid (18:2n-6) 1.7-fold ($p < 0.001$) and 6.9-fold ($p < 0.001$) in mild BA of controlled and partially controlled course of disease, respectively. In controlled moderate severity of BA, it has increased 3.7-fold ($p < 0.001$). However, with partially controlled BA of moderate severity, the proportion of linoleic acid (18:2n-6) has decreased 2.3-fold ($p = 0.003$) relative to the control.

The relative content of arachidonic acid (20:4n-6) has decreased by 80 % ($p < 0.001$) and 81 % ($p < 0.001$) in patients with mild BA with controlled and partially controlled course of disease, respectively. In patients with moderate BA, its content had no statistically significant differences comparing to the control group.

The assessment of the summary indicators of the FAs of mitochondrial membranes allowed establishing patterns of imbalance of these parameters in mild and moderate BA. Against the background of a decrease in the summary pool of SFAs, an increase by 13 % ($p < 0.001$) in the pool of summary indicators of n-6 PUFAs (summary PUFAs) has been revealed in mild severity-controlled BA, 3.7-fold ($p < 0.001$) – in mild severity partially controlled BA, and 2.3-fold ($p < 0.001$) – in moderate severity-controlled BA. In moderate severity partially controlled BA, the summary PUFA indicator has decreased by 41 % ($p < 0.001$).

A similar trend was observed in relation to the summary indicators of the MUFAs (summary MUFAs). Thus, in controlled and partially controlled mild BA, and in moderate severity-controlled BA, this parameter has increased by 13 % ($p < 0.001$), 265 % ($p < 0.001$), and 133 % ($p < 0.001$), respectively. With a partially controlled BA of moderate severity, the summary MUFAs has decreased by 41 % ($p < 0.001$).

DISCUSSION

The data obtained in the study indicate a modification of the FAs composition of mitochondrial membranes in patients with BA. However, the severity and tendency of these changes have certain specifics in the studied groups.

A pronounced deficiency of SFAs became common feature for all groups of patients with BA compared with the control group. (14:0, 16:0, 18:0, 20:0, 22:0). It is known that mitochondria obtain energy used preferably for oxidation of short-, medium-, and long-chain SFAs. In case of energy deficiency, mitochondria switch to use glucose as a substrate for β-oxidation [14-16]. A reduction in the concentration of saturated fatty acids in mitochondrial membranes can serve as an indicator of energy deficiency at the cellular level. A deficiency of SFAs leads to dysfunction of oxidative phosphorylation, which, in turn, initiates lipid peroxidation and phospholipolysis. These processes cause structural damage to mitochondrial membranes and can trigger apoptotic pathways that lead to cell death [8, 14, 17, 18].

Accumulation of monoenic acids in mitochondria, manifested by an increase in the proportion of oleic (18:1n-9) FA in mild BA, as well as erucic (22:1n-9) FA in mild BA and controlled BA of moderate severity, can be considered as a compensatory response. Another indicator of compensatory processes can be the production of n-6 PUFA, in particular, linoleic acid (18:2n-6) in mild BA and controlled BA of moderate severity.

However, with moderate BA, compensatory capabilities are likely being disrupted, which is manifested by a decrease in the content of oleic (18:1n-9) FA in moderate BA, as well as a decrease in the amount of erucic (22:1n-9) and linoleic (18:2n-6) FAs in patients with moderate BA with a partially controlled course of disease.

The PUFAs are precursors of the synthesis of oxylipins and specialized pro-resolving mediators, which are involved in the regulation of inflammatory responses [2, 19-22]. A significant decrease in the content of arachidonic acid in mild BA may indicate a reduction in the progression of the inflammatory process at these stages. It is known that arachidonic acid (20:4n-6) is a substrate for the synthesis of pro-inflammatory and bronchoconstrictor oxylipins (thromboxanes and leukotrienes), and increase in its content in membranes may be unfavorable prognosis of an increased pro-inflammatory response [23, 24].

The change in the ratio of FAs may be due to a change in their metabolism in the human body, carried out through the desaturation and elongation mechanisms. These processes are regulated by certain enzyme systems, whose activity can be assessed by FA metabolic transformation indicators. This concerns, in particular, desaturases involved in the biosynthesis of FAs. The ratio of FAs 18:1n9/18:0 reflects the activity of the Δ9 enzyme of desaturase [25]. With mild BA, this indicator has increased 2.9-fold ($p < 0.001$) and 3.6-fold ($p < 0.001$) in the controlled and partially controlled groups of patients, respectively. However, with moderate BA, the ratio of 18:1n9/18:0 has decreased by 60 % ($p < 0.001$) and by 28 % ($p < 0.001$) for controlled and partially controlled course of disease, respectively.

The obtained outcomes may indicate the activation of compensatory mechanisms in patients with mild BA and the depletion of these mechanisms in case of moderate BA.

CONCLUSIONS

The conducted study has shown that BA causes changes in the composition of FAs in the mitochondrial membrane. Against the background of a decrease in the amount of SFAs, the summary indicators of MUFAs

and n-6 PUFAs in mild BA of both controlled and partially controlled course of disease, as well as in controlled BA of moderate severity increase as a compensatory response. With partially controlled BA of moderate severity, compensatory capabilities are disrupted, which is manifested in a decrease in the total content of MUFAs and n6 PUFAs. This may indicate both the development of pathological processes underlying BA and the activation of compensatory mechanisms. Modification of the composition of mitochondrial FAs may become an important criterion for assessing the progression of BA.

Финансирование

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Conflicts of interest

Authors of this article declare no conflict of interest.

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