EFFECT OF THE NOS3 786C/T POLYMORPHISM ON THE LEVELS OF NITRIC OXIDE IN PATIENTS WITH ASTHMA AND COMORBID HYPERTENSION

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Nitric oxide has a significant role in the pathogenesis of bronchial asthma and hypertension. Its synthesis is catalyzed by NO synthases. The nucleotide composition of genes coding for these enzymes can affect their activity; therefore, it is important to understand the effect of the NOS3 786C/T polymorphism (rs2070744) on the blood levels of nitric oxide in patients with bronchial asthma and hypertension. Our study recruited 71 individuals. The main group consisted of 24 asthmatic hypertensive patients. Two comparison groups included patients with isolated asthma and isolated hypertension. All patients were genotyped for the NOS3 786C/T polymorphism. We measured total nitric oxide metabolites in their blood using a photocolorimetric technique and the Griess reagent. The levels of nitric oxide in the exhaled air were determined electrochemically using a portable NObreath monitor. The blood levels of nitric oxide metabolites amounted to 69.7 (60.0; 70.4) μmol/l in the CC genotype carriers, 68.9 (57.7; 77.4) μmol/l in the CT genotype carriers and 67.7 (59.7; 79.3) μmol/l in the patients with the TT genotype (p = 0.843). Individually, the groups demonstrated a clear association between the NOS3 786C/T polymorphism and the blood levels of nitric oxide metabolites. The patients with bronchial asthma and hypertension demonstrated a tendency to increasing nitric oxide levels following the pattern CC < CT < TT (p = 0.033 and p = 0.024, respectively). Thus, the C allele of the NOS3 786C/T polymorphism is associated with lower blood levels of nitric oxide metabolites in patients with bronchial asthma and hypertension.

Keywords: asthma, polymorphism, nitric oxide, hypertension

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ВЛИЯНИЕ ПОЛИМОРФИЗМА NOS3 786C/T НА УРОВЕНЬ ОКСИДА АЗОТА У КОМОРБИДНЫХ БОЛЬНЫХ БРОНХИАЛЬНОЙ АСТМОЙ И ГИПЕРТОНИЧЕСКОЙ БОЛЕЗНЬЮ

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В патогенезе бронхиальной астмы и гипертонической болезни значимую роль играет оксид азота, в синтезе которого участвуют ферменты NO-синтазы. Нуклеотидный состав генов может оказывать влияние на активность фермента, поэтому представляется актуальным изучение влияния полиморфизма гена NOS3 786C/T (rs2070744) на уровни оксида азота в крови и выдыхаемом воздухе у больных, страдающих бронхиальной астмой и гипертонической болезнью. В исследовании участвовал 71 пациент. В основную группу входили 24 пациента, страдающих одновременно бронхиальной астмой и гипертонической болезнью. Еще две группы сравнения включали больных с изолированной бронхиальной астмой и больных с изолированной гипертонической болезнью. У всех пациентов определяли полиморфизм NOS3 786C/T, измеряли уровень суммарных метаболитов оксида азота в крови фотоколориметрическим методом в реакции с реактивом Грисса и выявляли уровень выдыхаемой фракции оксида азота электрохимическим методом с помощью портативной тест-системы NObreath. Уровень метаболитов оксида азота в крови пациентов — носителей генотипа CC полиморфизма NOS3 786C/T составил 69,7 (60,0; 70,4) мкмоль/л, генотипа CT — 68,9 (57,7; 77,4) мкмоль/л, генотипа TT — 67,7 (59,7; 79,3) мкмоль/л (p = 0,843). В отдельных исследуемых группах была отмечена отчетливая связь полиморфизма NOS3 786C/T и уровня оксида азота в крови. У больных бронхиальной астмой и больных гипертонической болезнью уровень метаболитов оксида азота в крови достоверно нарастает в ряду CC < CT < TT (p = 0,033 и p = 0,024 соответственно). Таким образом, C-аллель полиморфизма NOS3 786C/T ассоциирована с более низким уровнем метаболитов оксида азота в крови больных, страдающих бронхиальной астмой и гипертонической болезнью.

Ключевые слова: астма, полиморфизм, оксид азота, гипертоническая болезнь

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Today, the scientific community is showing a growing interest in comorbidity since knowledge about comorbid conditions allows doctors to tailor treatment to an individual patient. Bronchial asthma, the second common respiratory disease, has a huge social impact. About half of patients with asthma also suffer from cardiovascular conditions, most importantly hypertension, which strikes 13–38% of asthmatic individuals [1]. Many aspects of this concomitance are still unclear, but the mutual impact between the two diseases is indisputable [2].

One of the possible mechanisms underlying this phenomenon is impaired synthesis of nitric oxide (NO), an intercellular signaling molecule [3]. Endothelium-derived NO modulates the vascular tone, blood flow and arterial pressure; abnormal production of nitric oxide leads to arterial hypertension and endothelial dysfunction [4–7]. Besides, NO regulates the airway tone and lumen; at small concentrations NO is protective against bronchial spasms and can be an important factor in asthma prevention [8–10].

In the human body NO is synthesized from L-arginine by a family of cytochrome P-450-type hemoproteins called nitric oxide synthases (NOS) which are represented by 3 isoforms: neuronal (nNOS), inducible (iNOS) and endothelial (eNOS) [5]. These isoforms are encoded by the genes *NOS1*, *NOS2* and *NOS3*, respectively. The endothelial synthase encoded by the *NOS3* gene contributes the most to the development of atherosclerosis, arterial hypertension and endothelial dysfunction. As its name suggests, this enzyme is found mainly in vascular endothelial cells. Under normal physiological conditions eNOS is a constitutive isoform; however, it is increasingly expressed in pathology, leading to the excess production of NO [11]. Nitric oxide produced by the constitutive synthase is essential for normal cell and tissue function. NO synthases exert their proinflammatory activity by catalyzing NO production in the early stages of inflammation. At the same time, they control biosynthesis of anti-inflammatory interleukins IL4, IL11, and IL13. Thus, NO synthases and nitric oxide they produce are “true” regulators of inflammation in bronchial asthma, among other conditions [12].

The level of NOS expression is directly dependent on the nucleotide composition of NOS-encoding genes. Therefore, the ability of NO to act either as a physiological regulator or a toxic agent is determined by the activity of NOS isoforms affected by the presence of mutations in the NOS-encoding genes. There has been a lot of research of polymorphisms in NOS genes and their role in pathology and nitric oxide synthesis. As a rule, individual polymorphisms have only a minor role in multifactorial diseases. There is no doubt that NO and NOS-coding genes are implicated in the pathogenesis of bronchial asthma and hypertension. However, their involvement in comorbidity is no so clear. Among the variety of NOS3 polymorphisms the most interesting is 786C/T (rs2070744) associated with coronary artery disease and myocardial infarction. These two conditions, as well as hypertension, are also associated with abnormal production of endothelial nitric oxide [13, 14]. The aim of this work was to study the effect of the NOS3 786C/T polymorphism on the levels of nitric oxide in the blood and exhaled air of patients with bronchial asthma and hypertension.

METHODS

The study was conducted at the Department of Intermediate Therapy of Ryazan State Medical University between 2014 and 2017 and was part of a dissertation research project [15]. The study was approved by the Local Ethics Committee of Ryazan State Medical University (Protocol 2 dated October 2, 2014) and complied with the Declaration of Helsinki and the standards of Good Clinical Practice.

The study recruited 71 inpatients of Ryazan Regional Clinical Hospital diagnosed with bronchial asthma or hypertension. The patients were distributed into 3 groups. The main group consisted of 24 patients with asthma and concomitant hypertension. Two comparison groups included patients with isolated asthma (n = 23) and patients with isolated hypertension (n = 24). The groups were comparable in terms of age and sex and comprised unrelated Caucasian individuals residing in Ryazan region. All patients gave voluntary informed consent to participate.

The study was conducted in men and women aged 45 to 69 years diagnosed with mixed asthma and/or hypertension based on the recommendations of the Global Initiative for Asthma and the Russian Society of Cardiology. The patients with bronchial asthma were included in the study only after the acute symptoms of the disease were alleviated and glucocorticoid drugs were discontinued or continued at maintenance doses (if the patients had been on those medications prior to hospital admission). Among the exclusion criteria were pregnancy and lactation, acute bronchial asthma, decompensated cardiovascular states, a previous history of psychosis or psychiatric conditions, a previous history of severe kidney/liver damage, other comorbidities that could have affected respiratory and cardiac functions or the parameters studied in our experiment, and alcohol abuse or drug addiction. In both groups, the patients with hypertension received similar treatment. The groups did not differ in the number of smokers (p = 0.441).

To measure total nitric oxide metabolites in the samples of blood serum, we applied a photocolorimetric technique modified by Metelskaya and used the StatFax 3200 microplate reader (Awareness Technology, USA) and the Griess reagent [16]. The levels of nitric oxide in the exhaled air (FeNO) were determined electrochemically using a portable NObreath monitor (Bedfont Scientific, UK) according to the manufacturer’s instructions. The NOS3 786C/T polymorphisms were genotyped in the Central Research Laboratory of Ryazan State Medical University by allele-specific PCR followed by gel electrophoresis of PCR products using reagents by Litech, Russia, and a thermocycler by DNA-Technology (Russia). For genotyping, DNA was isolated from whole blood leukocytes using the DNA-Express-Blood reagent kit by Litech, Russia. Distribution of the studied allelic variants in the sample was compared to their population frequency using the Hardy-Weinberg equilibrium.

The obtained data were processed in StatSoft Statistica 10. The normality of data distribution was evaluated by the Shapiro–Wilk test. The results are presented in this work as Me (Q25; Q75), where Me is the median and Q25 and Q75 are the upper and lower quartiles, respectively. The Kruskal–Wallis and Mann–Whitney tests were applied to evaluate the differences between the studied groups. The differences were considered significant at $p < 0.05$.

RESULTS

The genotype distributions and allele frequencies in the sample fell within the Hardy–Weinberg equilibrium ($\chi^2 = 0.08$, $p = 0.77$). We found that 12% of the participants had the CC genotype (n = 9), 44% had the CT genotype (n = 31), and 44% had the TT genotype (n = 31). The C allele of the NOS3 786C/T polymorphism was present in 35% of samples (n = 49), the T allele, in 65% of samples (n = 93). Previously we established that the T allele of NOS3 786C/T was more common in

Table 1. The levels of nitric oxide in the exhaled air in patients with different NOS3 786C/T genotypes

Genotype	BA and HT	BA	HT
CC	22 (15; 26)	11 (8; 13)	9 (9; 9)
CT	16 (13; 20)	16 (13; 20)	17 (13; 21)
TT	14 (9; 15)	20 (15; 23)	13 (8; 20)
p	0.184	0.062	0.356

Note: BA is bronchial asthma, HT is hypertension.

Table 2. The levels of nitric oxide metabolites in the blood of patients with different NOS3 786C/T genotype

Genotype	BA and HT	BA	HT
CC	59.5 (58.9; 60.0)	70.1 (69.7; 73.5)	43.9 (43.9; 43.9)
CT	68.1 (60.8; 72.0)	75.8 (70.1; 79.7)	55.6 (51.6; 57.7)
TT	79.3 (72.4; 84.3)	78.9 (77.0; 90.5)	60.4 (57.0; 65.4)
p	0.033	0.090	0.024

Note: BA is bronchial asthma, HT is hypertension.

asthmatic hypertensive patients than in patients with isolated bronchial asthma, suggesting that this polymorphism could be implicated in the concomitant development of asthma and hypertension [17].

We determined that median FeNO levels amounted to 15 (9; 23) ppb in the patients with the C genotype of the NOS3 786C/T polymorphism, 16 (13; 20) ppb in the carriers of the CT genotype, and 16 (9; 20) ppb in the patients with the TT genotype. The differences, however, were not statistically significant ($p = 0.834$) and fell within the range of measurement error for the NObreath test. Similar results were obtained for each studied group of our patients (Table 1).

The analysis of associations between NOS3 786C/T genotypes and blood levels of nitric oxide metabolites revealed that the median value of nitric oxide metabolites in the blood was 69.7 (60.0; 70.4) μmol/l for the CC genotype carriers, 68.9 (57.7; 77.4) μmol/l for the CT genotype carriers and 67.7 (59.7; 79.3) μmol/l for the patients with the TT genotype. The differences were statistically insignificant ($p = 0.843$) and consistent with our conclusions about the association between the NOS3 786C/T polymorphism and the development of asthma with comorbid hypertension [17]. Therefore, it seemed reasonable to assess the effect of the NOS3 786C/T polymorphism on the blood levels of nitric oxide metabolites in every studied group separately. For example, the patients in the main group and hypertensive individuals demonstrated a significant elevation of nitric oxide metabolites in the blood following the pattern CC < CT < TT ($p = 0.033$ and $p = 0.024$, respectively) (Table 2). A similar but less significant ($p = 0.090$) rise in the levels of nitric oxide metabolites was observed in the patients with bronchial asthma. To sum up, the obtained results drive us to the conclusion that the NOS3 786C/T polymorphism affects blood levels of nitric oxide metabolites, which are lower for C allele carriers and higher for T allele carriers.

DISCUSSION

The main problem obstructing the comprehensive study of the effect gene polymorphisms have on blood biochemistry in patients with bronchial asthma and hypertension is phenotypical heterogeneity. The disease phenotypes are associated with a broad range of changes in the biochemical blood composition and varying clinical symptoms, complicating the discovery of associations between gene polymorphisms and the severity of multifactorial diseases, including asthma and hypertension. This is the reason why the literature addressing this issue is scarce. A study of 121 SNPs in the genes coding for NOS1, NOS2, and NOS3 revealed an association between FeNO levels and the NOS3 polymorphism (rs743507, $p = 0.004$) [18]. However, the obtained results were highly heterogeneous. Another study looked at a possible association between the NOS3 786C/T polymorphism and the levels of nitric oxide metabolites in the blood of healthy young Russian men [19]. Just like the present research work, it established an association between the C allele of the NOS3 786C/T polymorphism and the low levels of nitric oxide and endothelial dysfunction. Therefore, we conclude that polymorphic variants of NOS1- and NOS3-encoding genes can affect nitric oxide production in patients with bronchial asthma and hypertension. Further investigation is needed, though, accounting for the disease phenotypes. Our study revealed no statistically significant effect of the polymorphism NOS3 786C/T on the levels of nitric oxide metabolites, but it did show that the carriers of the C allele tended to have lower metabolites, which is consistent with the published data on healthy individuals. High heterogeneity of asthma manifestations necessitates extensive research to establish a true association between the NOS3 786C/T polymorphism and the levels of nitric oxide and its metabolites in patients with bronchial asthma.

CONCLUSIONS

The C allele of the NOS3 786C/T polymorphism is associated with lower levels of nitric oxide metabolites in the blood of patients with asthma and comorbid hypertension. The levels of nitric oxide metabolites increase following the pattern CC < CT < TT in the blood of asthmatic hypertensive patients and patients with isolated hypertension ($p = 0.033$ and $p = 0.024$, respectively).

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