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Original Research

PHARMACOTHERAPY

Influence of β_2-Adrenergic Receptor Genotype on Airway Function During Exercise in Healthy Adults*

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Background: **In humans, β_2-adrenergic receptors (β_2ARs) influence airway tone. There are known functional polymorphisms of the β_2AR, such as substitution of glycine for arginine at codon 16. We sought to determine if this variation in genotype differentially influences airway function during exercise.**

Methods: **Healthy subjects without asthma who were either homozygous for Arg16 (n = 16; mean age, 29 ± 2 years [± SD]; mean maximum oxygen uptake [$\dot{V}O_2$], 32 ± 2 mL/kg/min) or the Gly16 allele (n = 26; mean age, 30 ± 1 years; mean maximum $\dot{V}O_2$, 33 ± 1 mL/kg/min) participated in the study. Baseline testing included spirometry and maximal symptom-limited exercise. On a separate day, an arterial cannula was placed to measure catecholamine levels. Subjects then performed exercise at two work levels (40% and 75% of peak work) for 9 min each and performed spirometry at 3-min intervals for assessment of airway function.**

Results: **There were no statistically significant differences between groups in maximum $\dot{V}O_2$ or baseline spirometry ($p > 0.05$). With both light and heavy exercise, the groups had similar increases in the forced expiratory flow at 50% of vital capacity (FEF_{50}). FEF_{50} increased by 14 ± 4% and 15 ± 3% in arginine and glycine groups, respectively, by end exercise ($p > 0.05$). During recovery (5 min and 10 min after), the Gly16 homozygotes demonstrated persistent bronchodilation (10 min after FEF_{50} = + 7 ± 2% over pre-exercise) while the Arg16 subjects had a rapid return to baseline (10 min after FEF_{50} = − 3 ± 3%, $p = 0.007$ between groups). No differences were observed in the catecholamine responses between genotypes, although the increase in epinephrine in the arginine group tended to be higher ($p = 0.07$).**

Conclusions: **These data suggest that the Arg16Gly polymorphism of the β_2AR does not influence airway function during short-duration low- and high-intensity exercise. However, during recovery, the Arg16 genotype is associated with a reduced bronchodilation, possibly due to increased catecholamine desensitization.** ***(CHEST 2006; 129:762–770)***

Key words: bronchodilation; catecholamines; genetic

Abbreviations: β_2AR = β_2 adrenergic receptor; bp = base-pair; CV = coefficient of variation; $FEF_{25–75}$ = forced expiratory flow at 25 to 75% of vital capacity; FEF_{50} = forced expiratory flow at 50% of vital capacity; GCRC = General Clinical Research Center; MEFV = maximal expiratory flow volume; PCR = polymerase chain reaction; SNP = single-nucleotide polymorphism; VC = vital capacity; $\dot{V}O_2$ = oxygen uptake; V_T = tidal volume

The respiratory system adapts to changes in metabolic demand in an attempt to maintain gas exchange homeostasis at minimal cost. Among the many respiratory adaptations that occur during exercise is exercise-induced bronchodilation, the mechanism of which remains controversial.[1,2] Changes in airway tone with exercise, although small, are important, as it allows for a large increase in ventilation without significant increases in airway resistance. Previous authors[2] have suggested that changes in airway tone with exercise occur mainly due to vagal withdrawal, while others[1,3] suggest this is primarily catecholamine mediated through the β_2-adrenergic receptor (β_2AR). Although the reported bronchodilation during exercise in healthy subjects can be variable, the result is a beneficial reduction in the flow-resistive work and oxygen cost of breathing.[2,4–7]

The β_2AR is a G protein-coupled receptor found

in airway smooth muscle from the trachea to the alveoli.[8] On catecholamine stimulation, the receptor goes through a conformational change that leads to an increase in cyclic adenosine monophosphate, which in turn activates protein kinase A. Protein kinase A transfers the terminal phosphate group of adenosine triphosphate to several target proteins, which leads to muscle relaxation.[9] The β_2AR is polymorphic. Specifically, an arginine → glycine substitution at codon 16 and a glutamine → glutamate substitution at codon 27 have been described.[10–12] Significant linkage disequilibrium exists between these sites so that typically when arginine is present at position 16 only glutamine is found at position 27.[13–15] *In vivo*, a study[16] in humans suggests that the homozygous Arg16Gln27 haplotype may be associated with an agonist-promoted desensitization in the venous circulation. Specifically, Gly16 homozygotes tend to show augmented blood flow when β-agonists are given in the brachial artery.[16]

The influence of the polymorphisms of the β_2AR on airway function is controversial, and studies[14,15,17–19] have primarily been limited to the asthmatic population. Responses observed in airway smooth muscle may also differ from those observed in blood vessels. Previously, Summerhill et al[20] found among Hutterites, that individuals homozygous for the Arg16 allele were found to have normal, although reduced, lung function relative to adults homozygous for the Gly16 allele. These differences were not observed in children, suggesting the Arg16Gly polymorphism may influence the rate of decline in lung function with aging.[20]

The focus of the present study was to determine if common polymorphisms of the β_2AR differentially influence airway tone during and after short-term exercise in healthy subjects without asthma. We hypothesized that subjects with homozygous Arg16 would have an attenuated bronchodilatory response at exercise intensities that induce catecholamine release (> 50% maximum workload).

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Materials and Methods

Subjects

The protocol was reviewed and approved by the Mayo Clinic Institutional Review Board, and all participants signed informed consent before entering the study. Age-, gender-, and activity-matched subjects were recruited from an existing pool of subjects who had previously been genotyped for the β_2AR as a part of a large study[13] of the genetic associations with BP. Forty-two individuals who were homozygous for arginine (Arg16, n = 16) or glycine (Gly16, n = 26) at codon 16, and had no exclusion criteria (cardiopulmonary abnormalities, pregnancy, inability to exercise) agreed to participate. All subjects were healthy nonsmokers, without asthma, and were not receiving any medications.

Protocol

Before performing the exercise protocols, subjects underwent baseline pulmonary function testing, an incremental cycle ergometry test to exhaustion, a CBC count (CBC, to rule out anemia), and in women a pregnancy test. The pulmonary function testing included postbronchodilator measures (albuterol) to assess baseline differences between genotypes in airway response to a β-agonist, and were determined according to current American Thoracic Society recommendations.[21] The baseline exercise study served as an initial familiarization session, was used to determine work intensities for subsequent sessions, and acted as a screening study to rule out ischemia and/or abnormal arrhythmias. Following these initial studies, subjects met with the General Clinical Research Center (GCRC) nutritionist and were put on a salt-neutral diet (3,450 mg/d) for 3 days with a 24-h urine collection to confirm sodium intake. A salt-neutral diet was used because previous studies[22,23] have suggested that the β_2AR may be sodium sensitive. Subjects subsequently returned to the GCRC on two occasions for exercise testing.

The next session consisted of a cycle ergometry test similar to the first visit. However, during this second study, classical gas exchange measures were collected and subjects also were instructed to perform maximal expiratory flow volume (MEFV) maneuvers at rest and over the last 30 s of each work level (every 2 min). Since most subjects were unfamiliar with the MEFV maneuver, this session served primarily as further familiarization with the measurements to be made on the final study day.

On the last visit, subjects exercised for 9 min at 40% and 9 min at 75% of their peak workload achieved during the initial exercise studies while gas exchange measurements were made and MEFV maneuvers were performed. During this session, a catheter was placed in the radial artery for sample collection taken just prior to performing the MEFV maneuvers for subsequent determination of catecholamines. The workloads of 40% and 75% of peak work were chosen in order to assess airway changes at a work intensity at which minimal catecholamine release would occur (< 50% maximum work) vs a work intensity at which substantial catecholamine release would be expected.

Data Collection

Blood Analysis: β_2AR genotyping was polymerase chain reaction (PCR) based according to methods of Bray et al.[13] Buffy coat, obtained from whole blood collected on ethylenediamine tetra-acetic acid, was extracted (Gentra Pure DNA isolation kit; Gentra Systems; Minneapolis, MN). Following extraction, DNA was treated with a proteinase K solution in preparation for PCR.