THE BROKEN BALANCE IN ASPIRIN INTOLERANCE

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Introduction

Acetylsalicylic acid-intolerant asthma (AIA) refers to the development of bronchoconstriction in asthmatic individuals following the ingestion of acetylsalicylic acid (ASA) and other nonsteroidal anti-inflammatory drugs (NSAIDs). This syndrome is characterized by aspirin hypersensitivity, bronchial asthma, and chronic rhinosinusitis with nasal polyposis, commonly named the »aspirin triad«. AIA affects about 5–10 % of adult asthmatics and is found more often in women. Although the pathogenesis of AIA is not completely understood, the cyclooxygenase theory is widely accepted. This theory proposes that asthma attacks by ASA and NSAIDs are triggered by the specific inhibition of cyclooxygenase (prostaglandin-endoperoxide synthase) in the respiratory tract, which is followed by a reduction of prostaglandin E2 (PGE2) and overproduction of cysteinyl leukotrienes (cysLTs). CysLTs are important inflammatory mediators in AIA and can mediate bronchoconstriction and increase mucus secretion, vascular permeability, and cellular infiltration cysLTs exert their biological action by binding two types of G-protein-coupled seven-transmembrane receptors, viz., cysteinyl leukotriene receptor 1 and CYSLTR2.
There is increasing evidence genetics might play important role in aspirin intolerance (AI). Sanak et al.[1] reported association between AIA and Single nucleotide polymorphism (SNP) in the promoter of LTC4S gene however this association was not replicated in other ethnic groups.[2]
In addition, few studies have been carried out on the gene polymorphisms of the enzymes in the arachidonic acid pathway in AIA, other than LTC4S and ALOX5. In this study, we have analyzed gene expression and SNPs of ALOX5, prostaglandin-endoperoxide synthase 2 (COX2), LTC4S, CYSLTR1 and CYSLTR2, and their haplotypes in AIA, ATA patients and normal controls in a Slovenian population in order to investigate the role of genetic polymorphisms of the candidate genes in AIA development.

Patients and methods

Thirthy Slovenian patients with aspirin intolerance (AI), fifty patients with nasal polyposis without AI, and 100 normal healthy controls has been be enrolled in the study. AIA was diagnosed by positive results on lysine-aspirin (L-ASA) bronchoprovocation tests. The L-ASA bronchoprovocation test was performed with increasing doses of aspirin (75–300 mg/ml, Aspirin, Bayer HealthCare AG, Germany) according to a modified method as previously described. All patients will perform skin prick tests with 12 common aeroallergens (Allergopharma). Atopy was defined as one or more positive reactions on skin prick test results. Normal controls were recruited from the general population who answered negatively to a screening questionnaire for respiratory symptoms, and had no past history of ASA hypersensitivity. All subjects gave informed consent to the studies, and the protocols were approved by the local ethics committees.
The participants underwent normal ENT procedures (nasal polypectomy and mucotomiam). Polyps were fixed in RNA later and stored at –20 °C. Approximately 15 mL of blood was obtained from each participant. Genomic DNA, RNA and proteins was extracted from peripheral blood leukocytes and nasal polyps using Tri reagent (Sigma). We used real time PCR and Taqman method for gene expression and SNP genotyping.

Results

We found significant correlation between SNPs and haplotypes in CYSLTR2 gene and AI patients, the frequencies of rare alleles –819T > G, 2078C > T, and 2534A > G were higher in subjects with AIA than in subjects with aspirin-tolerant asthma (P = 0.031). We have also found significant correlation between SNPs in COX2 gene and AI (p = 0.02). Pateints with G allele had lower COX2 expression in peripheral blood leucocytes (1.22±0.10, p = 0.03) and nasal polyps (0.38 ±0.10, p = 0.01) as compared to controls (1.96±0.30) and nasal polyps in ATA (2.220.38 ±0.10). The allele frequency for SNP in the promoter of

LTC4S gene (–444 A > C) was lower for the C allele in patients with AIA (0.150) as compared to ATA group (0.192) and controls (0.200).

Conclusion *We confirmed associations between SNPs in COX2, CYSLTR2 and LCT4S genes and Slovenian AI patients.*

References

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