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Title: Formoterol-induced downregulation of the beta2-adrenoceptor in asthmatics with homozygous glycine-16 polymorphism

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Body: Polymorphism at codon 16 of the beta2-adrenoceptor (beta2-AR) affects the responsiveness to salmeterol in asthmatics. Data concerning formoterol are more controversial in literature. The aim of this study was to verify whether homozygous for arginine-16 (ArgArg16) and homozygous for glycine-16 (GlyGly16) genotypes differently influence the long-term responsiveness to formoterol. Twenty-nine patients with mild-to-moderate asthma, in stable clinical conditions, underwent genotyping at codon 16 of the beta2-AR by RFLP-PCR assay and performed baseline respiratory function tests. The effects of a 4-week mono-therapy with formoterol (12 mcg BID) were tested on the peak expiratory flow (PEF) variability and the forced expiratory volume in 1 sec (FEV1) slope of the dose-response curve to salbutamol. According to the genotypic analysis, 14 patients were GlyGly16, 5 were ArgArg16, and 10 were heterozygous ArgGly16. Variability in PEF significantly increased during the 4-week treatment period in GlyGly16, but not in pooled ArgArg16 and ArgGly16 patients (p=0.032). The FEV1 slope of the dose-response curve to salbutamol decreased in GlyGly16, but not in pooled ArgArg16 and ArgGly16 patients. This study provides preliminary evidence that tolerance to formoterol develops more frequently in asthmatics carrying the GlyGly16 genotype. If confirmed in a larger population, this finding might be introductory to choose formoterol or salmeterol on the basis of genetic polymorphism at codon 16 of the beta2-AR.