

Effect of genotype on responses to enantiomers and the significance of the eudismic analysis in asthma research

To the Editor:

I read with interest the article by Ameredes and Calhoun¹ on advances in asthma research. Unfortunately, the authors did not take into account the haplotypes of the donors and did not present the results of the eudismic analysis.

In asthma, the response to β -agonists acting at β_2 -adrenergic receptors (β_2 ARs) displays extensive interindividual variation, in part because of genetic variation in the β_2 AR genotypes. β_2 -Adrenergic polymorphisms might have influenced the treatment effect in this study mainly for 2 reasons:

- β -Agonist-induced changes in inflammatory gene expression may be higher in cells from donors with β_2 AR having certain haplotypes. In a study by Flynt et al.,² Arg16/Gln27 β_2 AR released more proinflammatory IL-6 and vascular endothelial growth factor when stimulated with racemic isoproterenol, but when bypassing the β_2 AR, the response was unaffected by haplotype. Isoproterenol induced release of IL-6, and vascular endothelial growth factor was highest in Arg16/Gln27 cells, moderate in Gly16/Glu27 cells, and lowest in Gly16/Gln27 cells.
- A nonsynonymous adenylyl cyclase type 9 polymorphism, which results in substitution of Met for Ile at amino acid 772, can predict β -agonist efficacy in the absence and presence of corticosteroid treatment.³ Cells cultured in the presence of glucocorticoid expressing Met772 had a significantly increased albuterol-stimulated adenylyl cyclase response (approximately 80%) when compared with those expressing Ile772 (approximately 20%; $P = .02$).

When comparing the stereoselective bioactivity of enantiomers for characterizing their opposed properties, the results of both the eudismic analysis (the correlation between the potency of the racemic drug and the ratio of its isomers' potencies) and the purity of the distomer preparation need to be presented. In the case of albuterol, the eutomer-to-distomer binding affinity ratio at the β_2 AR may be as high as 500 to 1000.⁴ At this ratio, even minute traces of eutomer, as low as 0.1% of the total amount of distomer, may cut in half the apparently opposed pharmacologic activity of the distomer preparation.

In conclusion, as long as the haplotypes of the 3 donors and the degree of enantiomeric purity are not known, the results of the pharmacologic characterization of chiral compounds are in doubt, and we are cautious about the conclusions regarding chiral aspects of structure-activity relationships.

Mihai-Sergiu Jalba, MD, PhD
Postdoctoral Research Fellow

From the Health Services Research Postdoctoral Fellowship Program, Division of Research, Department of Family Medicine, Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey, Piscataway, NJ; 1715 Woodbine St, Apt 3R, Ridgewood, NY 11385.

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Reply

To the Editor:

We thank Dr Jalba¹ for his comments regarding our recently published article,² in which he questioned the potential for β_2 -adrenoceptor and adenylyl cyclase polymorphisms and the eudismic ratio of enantiomers as possible variables that might have influenced the observed results of our studies. We recognize that full characterization and understanding of β_2 -adrenoceptor effects can include haplotype determination.³ Likewise, this applies to the assertions raised regarding the adenylyl cyclase type 9 polymorphism.⁴ We would agree that, if possible, a haplotype analysis might be desirable, and that caution should be exercised in the broad application of our results across all donors and cells. Furthermore, as pointed out by Dr Jalba, both in this letter to the editor,¹ and his previous one⁵ regarding the work of Agrawal et al,⁶ the eudismic ratio is an important consideration in the evaluation of results obtained with enantiomeric compounds, because it describes the levels of contamination of the distomer with the eutomer.⁷

However, we disagree with the assertion that the results of the pharmacological characterization of chiral compounds are in doubt, for the following reasons. First, our albuterol enantiomers came from the same lot as those of Agrawal et al,⁸ such that the (S)-albuterol hydrochloride was 99.93% pure, whereas the (R)-albuterol hydrochloride was 99.88% pure. This was an error of omission within our publication² that we appreciate the opportunity to correct. However, under those circumstances, it would be unlikely that the effects we reported as a result of (S)-albuterol would be a function of contamination with 0.02% of the minor isomer, particularly if the (S)-albuterol effects are caused by intracellular binding on organelles within human airway smooth muscle cells (HASCs),