References

1. Thanawala VJ, Forkuo GS, Al-Sawalha N, Azzegagh Z, Nguyen LP, Eriksen JL, Tuvim MJ, Lowder TW, Dickey BF, Knoll BJ, *et al.* β_2 -Adrenoceptor agonists are required for development of the asthma phenotype in a murine model. *Am J Respir Cell Mol Biol* 2013;48:220–229.
2. Lee DK, Currie GP, Hall IP, Lima JJ, Lipworth BJ. The arginine-16 beta2-adrenoceptor polymorphism predisposes to bronchoprotective subsensitivity in patients treated with formoterol and salmeterol. *Br J Clin Pharmacol* 2004;57:68–75.
3. Wechsler ME, Kunselman SJ, Chinchilli VM, Bleecker E, Boushey HA, Calhoun WJ, Ameredes BT, Castro M, Craig TJ, Denlinger L, *et al.*; National Heart, Lung and Blood Institute's Asthma Clinical Research Network. Effect of beta2-adrenergic receptor polymorphism on response to longacting beta2 agonist in asthma (LARGE trial): a genotype-stratified, randomised, placebo-controlled, crossover trial. *Lancet* 2009;374:1754–1764.
4. Bleecker ER, Nelson HS, Kraft M, Corren J, Meyers DA, Yancey SW, Anderson WH, Emmett AH, Ortega HG. Beta2-receptor polymorphisms in patients receiving salmeterol with or without fluticasone propionate. *Am J Respir Crit Care Med* 2010;181:676–687.
5. Basu K, Palmer CN, Tavendale R, Lipworth BJ, Mukhopadhyay S. Adrenergic beta(2)-receptor genotype predisposes to exacerbations in steroid-treated asthmatic patients taking frequent albuterol or salmeterol. *J Allergy Clin Immunol* 2009;124:1188–1194 e1183.
6. Lipworth BJ, Basu K, Donald HP, Tavendale R, Macgregor DF, Ogston SA, Palmer CN, Mukhopadhyay S. Tailored second-line therapy in asthmatic children with the Arg(16) genotype. *Clin Sci (Lond)* 2013;124:521–528.

Copyright © 2013 by the American Thoracic Society

Reply: Adverse Effects of Long-Acting Beta-Agonists on Airway Hyperresponsiveness

From the Authors:

In their letter, Lipworth and colleagues raise an interesting point and we welcome their suggestion that our work in murine asthma models may help understand a clinically important point (1). We fully concur with the idea that a patient's β_2 -adrenoceptor (β_2 AR) genotype may increase their susceptibility to adverse effects of β_2 AR agonists. Lipworth and colleagues suggest our data are consistent with their finding that individuals with the arginine-16 polymorphism have enhanced airway hyperresponsiveness following exposure to the high-efficacy β_2 AR agonist formoterol (but not the low-efficacy agonist salmeterol) (1); they also raise concerns with the recently developed high-efficacy ultra-long-acting β_2 AR agonists, like indacaterol and vilanterol. Lipworth and colleagues conclude by suggesting that the likely explanation for this observation is that the arginine-16 polymorphism enhances the higher rates of desensitization and down-regulation that have been shown to be produced by high-efficacy β_2 AR agonists (2).

We fully concur that this pharmacological principle, of a significant correlation between ligand efficacy and desensitization and down-regulation, is the Occam's razor explanation for the clinical findings and must be ruled out before introducing complex alternatives. However, we wish to point out that in wider

studies, the uniqueness of formoterol over salmeterol in producing adverse effects has not been observed, and the FDA guidelines have labeled them with identical precautions and warnings. A more inclusive, albeit more speculative, explanation may be that the arginine-16 polymorphism results in preferential trafficking of the formoterol occupied β_2 AR to an alternate pathway than the canonical G_s -cAMP-PKA signaling. In asthma we suggest β_2 AR signaling via β -arrestin is the alternate pathway promoting airway hyperresponsiveness and inflammation (3, 4). Preferential pathway activation resulting from a specific ligand (ligand bias) is well documented as an ability of the ligand to form a binary complex with the receptor producing a conformation that results in biased pathway activation (4). Here we simply suggest that a structural change in the other component of the binary complex, the receptor, is now responsible for conferring the bias.

Finally, we would like to add that there is an intrinsic weakness to the desensitization/down-regulation hypothesis. While it is true that high-efficacy ligands produce greater loss of receptor function and number in comparison to low-efficacy ligands that produce minimal alterations in receptor function and numbers, it is also true that high-efficacy ligands require less occupied receptors to produce their effects. Thus, from a receptor theory point of view, these effects tend to cancel each other out, and that is why both strategies have been employed and rationalized by different pharmaceutical companies.

Author disclosures are available with the text of this letter at www.atsjournals.org.

GLORIA S. FORKUO, B.PHARM
VAIDEHI J. THANAWALA, M.S.
NOUR AL-SAWALHA, PHARM.D.
RICHARD A. BOND, PH.D.
University of Houston
Houston, Texas

JULIA K. L. WALKER, PH.D.
Duke University Medical Center
Durham, North Carolina

References

1. Lee DK, Currie GP, Hall IP, Lima JJ, Lipworth BJ. The arginine-16 beta2-adrenoceptor polymorphism predisposes to bronchoprotective subsensitivity in patients treated with formoterol and salmeterol. *Br J Clin Pharmacol* 2004;57:68–75.
2. Clark RB, Knoll BJ, Barber R. Partial agonists and G protein-coupled receptor desensitization. *Trends Pharmacol Sci* 1999;20:279–286.
3. Drake MT, Violin JD, Whalen EJ, Wisler JW, Shenoy SK, Lefkowitz RJ. Beta-arrestin-biased agonism at the beta2-adrenergic receptor. *J Biol Chem* 2008;283:5669–5676.
4. Walker JK, Penn RB, Hanania NA, Dickey BF, Bond RA. New perspectives regarding $\beta(2)$ -adrenoceptor ligands in the treatment of asthma. *Br J Pharmacol* 2011;163:18–28.

Copyright © 2013 by the American Thoracic Society