Far from "Disappointing"

To the Editor:

I was rather surprised by the study by Short and coworkers published in the June 15, 2013, issue of the *Journal* (1), and the accompanying Editorial that concludes that the findings that chronic propranolol treatment failed to alter methacholine or histamine reactivity, or other features of the asthma phenotype, "are disappointing from a therapeutic perspective" (2).

In reality, these results are actually encouraging in the quest to identify the optimal β_2-adrenoceptor (β_2AR)-regulating ligand. Recent advances in our understanding of G protein–coupled receptor biology and pharmacology reveal a complexity of receptor signaling properties that enable a great diversity in the effects of various ligands. An interpretation more consistent with our current understanding of β_2AR signaling complexity is that propranolol lacks the key property of a "β-blocker" that enables protection against the development of the allergic asthma phenotype.

Early studies by the Bond laboratory suggested that *inverse agonism* of the β_2AR was key to the therapeutic actions of certain β-blockers such as nadolol. Presumably, this interpretation influenced the design of the current propranolol trial; propranolol is an inverse agonist of the β_2AR, and thus propranolol might be assumed to be the therapeutic equivalent of nadolol. Unfortunately, inverse agonism is not the property that mediates the inhibitory actions of certain β-blockers on asthma.

Whereas receptor antagonism defines the ability to inhibit only the receptor activated by ligand, inverse agonism defines the ability to inhibit constitutive (unliganded) receptor activity. The Bond group originally reported that in an ovalbumin mouse model, chronic administration of the β_2AR antagonist alprenolol had no effect, the partial inverse agonist carvedilol had a modest effect in reversing ovalbumin-induced airway hyperreactivity, and the full inverse agonist nadodol was most effective in reversing airway hyperreactivity (3). Although these findings suggest a role for inverse agonism, they provide evidence of correlation, not causation. The evidence that conclusively buries the inverse agonism argument comes from a study last year by Bond and colleagues (3) which demonstrates that depleting systemic epinephrine in mice is sufficient to inhibit the development of allergen-induced asthma. Thus, β_2AR activation by ligand, and not constitutive (unliganded) β_2AR activity, appears permissive for asthma pathogenesis, meaning that inverse agonism is not the critical property mediating the protective actions of certain β-blockers.

Recently, a more attractive explanation has emerged. Studies into the mechanisms mediating the efficacy of β-blockers in the treatment of congestive heart failure (CHF) point to *ligand bias*—the ability of ligand to selectively promote specific intracellular signaling events—as an important property in useful CHF drugs. With respect to CHF, β-blockers that inhibit G protein signaling, but *activate G-protein–independent signaling* (perhaps arrestin- or ERK-dependent), may be more effective. Interestingly, the opposite may be true for "β-blockers" in the treatment of asthma, given that β-arrestin2 gene ablation inhibits the asthma phenotype, and that Gs/cAMP/PKA is believed to antagonize multiple features of asthma (reviewed in Reference 5). Indeed, the growing appreciation of the role of biased agonism in dictating functional consequences of G protein–coupled receptors, along with the characterization of ligand bias for multiple βAR ligands, prompted Bond and coworkers in 2011 to acknowledge the more likely role of ligand bias in the protective actions of certain β-blockers in asthma (5).

With this knowledge, along with the published characterization of clear differences in signaling profile between propranolol and nadolol (6, 7), propranolol is a questionable choice of ligand to test in a clinical trial if one hopes to validate the therapeutic utility of a "β-blocker." Admittedly, more basic science and pre-clinical research into the beneficial/detrimental signaling events mediated by β_2AR that impact the asthma phenotype needs to be performed to clarify the optimal β_2AR ligand to test in clinical trials. Until that time, responsible clinical research into this question should focus on the one β_2AR ligand with a consistent effect demonstrated across multiple asthma models: nadolol. ■

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

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Reply: Pharmacological Obfuscation of Clinical Relevance

From the Authors:

Bond and Penn provide an eloquent pharmacological perspective to explain why propranolol may have failed to improve airway