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The Intrinsic Bias of Generalizations*

To the Editor:

The article by Short and colleagues in the June 15, 2013, issue of the *Journal* demonstrates that propranolol is not effective in treating a subset of individuals with asthma (1). This study and the accompanying editorial from Kazani and Israel (2) express concern about the validity of the hypothesis that certain β-blockers may be useful in chronic asthma therapy. The Editorial concludes: "For now, in the case of β blockers in asthma, what doesn't kill you does not appear to make you stronger" (2). However, both publications treat "β blockers" as a class, or at best recognizing only inverse agonists and antagonists. This simplification does not acknowledge the complexities of β_2-adrenoceptor (β_2AR) signaling (3). Clinical studies exemplified this complexity when only certain β-blockers were shown to be beneficial in the chronic treatment of congestive heart failure (CHF).

The β_2AR signals via at least two distinct pathways: the canonical Gs-cAMP pathway, and signaling via β-arrestin and/or extracellular signal–regulated kinases (ERK) activation (4). The endogenous ligand for the β_2AR, epinephrine, and β_2AR agonists used in asthma therapy like albuterol, salmeterol, and formoterol, activate both pathways (5). However, it is now known some ligands preferentially activate one pathway over the other. These ligands are termed "biased ligands." Further, certain β-blockers can shut down one pathway while activating the alternate one, and β_2AR ligand bias has been shown for β-blockers as well as for β_2AR agonists. Indeed, Lefkowitz and colleagues have proposed that it is carvedilol's ability to activate β-arrestin signaling while shutting down the canonical Gs-cAMP pathway that results in the drug's superior efficacy in the treatment of CHF (6). However, as in CHF, differential β_2AR signaling appears to be important in asthma. Thus, several *in vitro* and *in vivo* studies suggest that β-arrestin/ERK signaling is detrimental in asthma (3, 7). This includes data showing that carvedilol (but not nadolol) increased methacholine sensitivity in the original 2004 murine studies investigating the hypothesis of "chronic use of β-blockers in asthma" (8). Thus the signaling signature produced by carvedilol, the gold standard in the treatment of heart failure, is not likely to be beneficial in asthma.

The data regarding dual β_2AR signaling pathways and biased ligands predicts that nadolol and propranolol would have different effects in asthma treatment. Specifically, various studies have shown that propranolol is a biased ligand similar to carvedilol; it activates β-arrestin and/or ERK signaling while shutting down the canonical pathway (3, 6). These studies also showed that nadolol differs from carvedilol and propranolol in that it shuts down β-arrestin/ERK (3, 6). Thus, one would not expect that studies showing benefit using nadolol would be repeated using propranolol. The article by Short and coworkers, and the Editorial by Kazani and Israel, provide some suggestions for alternate explanations of the study with propranolol, but the implied take-home message (as evidenced by the title and concluding sentence of the Editorial) is that the use of β-blockers in asthma is unlikely to be of benefit. This is unfortunate, because the negative outcome using propranolol is exactly what current receptor knowledge would predict. In a very real sense, the study by Short and colleagues provides some of the best clinical data supporting current hypotheses regarding β_2AR signaling and biased ligands.

The stunning success of carvedilol in CHF might never have been realized if the ineffectiveness of bucindolol had further biased the field against β-blockers by publishing first. There is currently an active multi-center, double-blind, placebo-controlled clinical trial using nadolol in subjects with mild asthma, funded by the National Institutes of Health/National Institute of Allergy and Infectious Diseases (ClinicalTrials.gov Identifier: NCT01804218). Hopefully, like the current report, those results will also add compelling data to support or negate the hypothesis that nadolol, but not propranolol, could be of benefit in asthma therapy. ■

*The title is based on sections from Malcolm Gladwell's book, *What the Dog Saw*, about common, incorrect generalizations, and their consequences.

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