

Correspondence

Non-canonical β_2 -receptor signaling

To the Editor:

We read with interest the recent review on β -adrenergic theory in asthmatic patients.¹ We believe the authors might have omitted some important points that are worthy of mention, especially the role of non-canonical pathways involved in β_2 -receptor signaling.

First, as clinicians, we have to deal with the apparent paradox that long-acting β -agonists (LABAs) can worsen asthma control when used on their own but not when combined with inhaled corticosteroids (ICSs). LABAs might exhibit proinflammatory effects acting through non-canonical G protein cyclic AMP-independent pathways that involve extracellular signal-regulated kinase 1/2 and β -arrestin. Treating adrenaline-depleted antigen-sensitized mice with formoterol induces an inflammatory asthmatic phenotype.² This might perhaps infer that switching off β -receptor signaling with an inverse agonist might confer beneficial effects in asthmatic patients as opposed to stimulation with LABAs. This concept was reinforced by evidence in β_2 -receptor knockout mice who do not have antigen-induced airway hyperresponsiveness or other asthmatic inflammatory characteristics, with the same effect being achieved in wild-type mice treated with the inverse agonist nadolol.³ To date, there are no placebo-controlled studies with nadolol that have shown such protective effects in ICS-treated or naive asthmatic patients.

The US Food and Drug Administration-mandated studies have provided reassurance regarding the use of ICS/LABA

combination inhalers. Nonetheless, it still leaves clinicians with the somewhat uneasy alliance of ICSs and LABAs in terms of the salutary effects of ICSs protecting against the potentially adverse effects of LABAs.

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Disclosure of potential conflict of interest: B. Lipworth reports personal fees and equipment as an unrestricted educational loan from Thorasys; grants, personal fees, and nonfinancial support from Chiesi; and grants and personal fees from Teva in relation to the present study and grants, personal fees, and nonfinancial support from Boehringer Ingelheim and personal fees from Sanofi, Novartis, Cipla, Circassia, Vectura, Glenmark, Dr Reddys, Lupin, Genentech, and Circassia outside the submitted work. C. R. Kuo reports personal fees from AstraZeneca outside the submitted work. R. Chan declares that he has no relevant conflicts of interest.

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<https://doi.org/10.1016/j.jaci.2019.08.017>