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LETTER TO THE EDITOR

From mouse to man: predicting biased effects of beta-blockers in asthma

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LINKED ARTICLES

This article is a Commentary on Thanawala VJ, Valdez DJ, Joshi R, Forkuo GS, Parra S, Knoll BJ, Bouvier M, Leff P and Bond RA (2015). Beta-blockers have differential effects on the murine asthma phenotype. Br J Pharmacol 172: 4833–4846. doi: 10.1111/bph.13253. The authors reply in Bond RA, Thanawala VJ, Parra S and Leff P (2016). Differences in asthma study models and the effectiveness of β_2-adrenoceptor ligands: response to Lipworth *et al*. Br J Pharmacol 173: 250–251. doi: 10.1111/bph.13334.

Tables of Links

TARGETS
Enzymes
ERK1/2

LIGANDS	
Adrenaline	Nadolol
Histamine	Propranolol
Methacholine	

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Pawson *et al.*, 2014) and are permanently archived in the Concise Guide to PHARMACOLOGY 2013/14 (Alexander *et al.*, 2013).

We read with interest the elegant data from Thanawala *et al*. (2015) in ovalbumin-sensitized adrenaline-deficient or wild-type mice, which suggested differential effects of biased signalling with propranolol and nadolol. We were particularly intrigued by the observation in adrenaline-deficient mice that there was a disconnect between propranolol and nadolol in restoring the asthma phenotype compared with controls. It is tempting to simplistically extrapolate these data in mice to what might happen in human subjects with asthma in order to explain the negative effects of propranolol on airway hyper-responsiveness (AHR), reported in two separate placebo-controlled double-blind trials in patients receiving inhaled corticosteroids (ICS), which were powered to detect a one doubling dilution difference in the provocative concentration of methacholine (n = 18) or histamine (n = 16) to produce a 20% fall in forced expiratory volume in 1s (i.e. the PC20 FEV1 threshold) (Short *et al.*, 2013; Anderson *et al.*, 2014). In this regard, in patients with persistent asthma, the PC threshold for FEV1 is closely related to PC threshold for airway resistance (Short *et al.*, 2015).

Upon close inspection of the data for methacholine AHR (Thanawala *et al.*, 2015), the provocative concentration to induce a 100% increase (PC100 threshold) in airway resistance was unaltered in wild-type mice (n = 6) treated with propranolol in contrast to an increase with nadolol (n = 7). The blunting of methacholine AHR with nadolol which was statistically significant ($P < 0.05$) amounted to approximately a 0.6 doubling dilution shift compared with vehicle-treated mice (n = 10). Such an effect in mice with nadolol on AHR would be considered clinically irrelevant in human patients as it less than the minimal important difference of one doubling dilution shift in PC threshold. It is therefore difficult to extrapolate the magnitude of this effect with nadolol on methacholine AHR in mice to what has previously been reported in two unblinded studies with nadolol in human asthmatic subjects which amounted to an approximate two doubling dilution shift in methacholine PC20, albeit in mild intermittent asthmatics who were not taking ICS (Hanania *et al.*, 2008; Hanania *et al.*, 2010).

It is however unclear how the relative mg per body weight dose of propranolol in mice (80–140 mg·L^{-1} in water) equates to that in humans (80 mg slow release tablet per day). Moreover, if propranolol at usual therapeutic doses of 80 mg per day does indeed confer arrestin-independent, partial agonist activity at the ERK1/2 activation pathway in humans, then one might expect to see an increase in Th2-mediated inflammatory biomarkers. For example, in persistent asthmatics, there was no worsening in eosinophils, eosinophilic cationic protein or exhaled breath NO when oral propranolol 80 mg per day was added to a low dose of ICS, while a higher dose of ICS in conjunction with oral placebo produced further suppression of the same Th2 biomarkers (Anderson *et al*., 2014). Moreover, asthma control and disease-specific quality of life were also unaltered by propranolol (Short *et al*., 2013; Anderson *et al*., 2014).

In order to properly confirm the putative beneficial effects of biased inhibitory signalling in mice, this will require a placebo-controlled trial to demonstrate clinically relevant improvements in methacholine PC20, inflammatory markers and asthma control with nadolol on top of existing ICS therapy in persistent asthma. The placebo-controlled clinical trial (clinicaltrials.gov NCT01804218) evaluating effects of nadolol in ICS naïve mild intermittent asthmatics will unfortunately not answer this clinically important question.

Conflict of interest

BJL has received previous grant support from the Chief Scientist Office, Scotland, to evaluate effects of propranolol in patients with persistent treated asthma. BJL has also received unrestricted grant support from Chiesi, Meda, Almirall and Teva to evaluate small airways in persistent asthma and COPD; as well as multicentre pharmaceutical support from Astra Zeneca, Teva, Janssen and Roche. In addition, BJL has received personal payment for consultancy and advisory boards with the following pharmaceutical companies: Astra Zeneca, Chiesi, Teva, Boehringer Ingelheim and Meda. BJL has also received personal payment for giving speaker talks with Chiesi, Teva, Meda and Mitsubishi Tanabe as well as support to attend educational meetings from Chiesi, Boehringer Ingelheim and Teva. WJA and PMS have no conflict of interest.

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