British Journal of Pharmacology

DOI:10.1111/bph.13334
www.brjpharmacol.org

LETTER TO THE EDITOR

Differences in asthma study models and the effectiveness of β_2-adrenoceptor ligands: response to Lipworth *et al.*

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Received
14 September 2015
Accepted
14 September 2015

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LINKED ARTICLES

This article is a reply to Lipworth BJ, Anderson WJ and Short PM (2016). From mouse to man: predicting biased effects of beta-blockers in asthma. Br J Pharmacol 173: 248–249. doi: 10.1111/bph.13335, commenting 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.

Tables of Links

TARGETS
GPCRs[a]
β_2-adrenoceptors
Enzymes[b]
PKA

LIGANDS
Nadolol
Propranolol

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 ([a b]Alexander *et al.*, 2013a,b).

We thank Lipworth *et al.* (2016) for their positive comments about our work. We agree with the letter that animal models of a disease have many limits compared with the human disease and can have additional substantial shortcomings such as dosing comparisons and not being representative of the spectrum of disease severity (Lipworth *et al.*, 2016). The reason we discussed the different outcomes of clinical trials using propranolol or nadolol in our study is that, given the different signalling profiles of these compounds (Wisler *et al.*, 2007; Walker *et al.*, 2011), there is no reason to expect the same results or assume the generalizations that were discussed in the original propranolol report (Short *et al.*, 2013). It seems to us the published differences in signalling would be a highly likely explanation for the differences between clinical trials using propranolol and nadolol (Hanania *et al.*, 2008; Short *et al.*, 2013), but this alternative was not considered in the original propranolol study (Short *et al.*, 2013). Our study also shows that the signalling differences first documented in cell-based assays also have *in vivo* relevance in an animal model of airway disease and are consistent with the differences observed in the clinical trials using propranolol or nadolol (Thanawala *et al.*, 2015). Indeed, we are now fortunate enough to have a situation where the spectrum of data includes mathematical modelling, cell-based studies, *in vivo* studies in an animal model of disease and clinical trials, and all are supportive of current receptor theory (Wisler *et al.*, 2007; Hanania *et al.*, 2008; Short *et al.*, 2013; Thanawala *et al.*, 2015). However, we agree

that other possibilities discussed by Lipworth and colleagues may contribute to the observed discrepancy. We also agree that further experiments are needed but suggest that, rather than study nadolol and propranolol clinically to 'prove' a point, future research prompted by evidence from all sides would be to discover and investigate selective/preferential β_2-adrenoceptor ligands that lack ERK1/2 activation and differ in their activity at the canonical cAMP–PKA pathway. Finally, given our experience with what happened in the treatment of congestive heart failure, where only two of the various 'β-blockers' tested showed therapeutic efficacy and received FDA approval, we believe it is time to stop the generalized expectation that these drugs will have class effects in all diseases, as they clearly have a spectrum of signal-modifying properties.

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