



University of Dundee

Of mice and men-the curious tale of β blockers in asthma

Lipworth, Brian; Jabbal, Sunny

Published in:
The Lancet Respiratory Medicine

DOI:
[10.1016/S2213-2600\(16\)00011-4](https://doi.org/10.1016/S2213-2600(16)00011-4)

Publication date:
2016

Document Version
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

Citation for published version (APA):
Lipworth, B., & Jabbal, S. (2016). Of mice and men-the curious tale of β blockers in asthma. *The Lancet Respiratory Medicine*, 4(2), 89-91. [https://doi.org/10.1016/S2213-2600\(16\)00011-4](https://doi.org/10.1016/S2213-2600(16)00011-4)

General rights

Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Manuscript Number: THELANCETRM-D-16-00009R1

Title: Of mice and men - the curious tale of beta-blockers in asthma

Article Type: Comment

Keywords: asthma, inverse-agonist, beta-blocker, airway hyperresponsiveness

Corresponding Author: Prof. Brian Lipworth, MD

Corresponding Author's Institution: University of Dundee

First Author: Brian Lipworth, MD

Order of Authors: Brian Lipworth, MD; Sunny Jabbal, MBChB

Manuscript Region of Origin: UNITED KINGDOM

Abstract: N/A

Of mice and men – the curious tale of beta-blockers in asthma

Dr Brian Lipworth & Dr Sunny Jabbal

Scottish Centre for Respiratory Research

School of Medicine

University of Dundee

Ninewells Hospital and Medical School

Dundee, DD1 9SY

Correspondence: b.j.lipworth@dundee.ac.uk

Word count = 853

Key Words: asthma, inverse-agonist, beta-blocker, airway
hyperresponsiveness

Declaration of interests

Dr. Lipworth reports personal fees and non-financial support from Boeringher Ingelheim, personal fees from Cipla, personal fees from Sandoz, grants and personal fees from Chiesi, grants and personal fees from Teva, grants and personal fees from Meda, personal fees from Dr Reddys, grants from AstraZeneca, grants from Roche, grants from Janssen, grants from Pearl, non-financial support from Thorasys, outside the submitted work.

Dr Jabbal has no conflict of interest to declare.

Stimulation of airway β 2-adrenoceptors (β 2ADR) by short or long acting agonists (LABA) via the classical (canonical) G protein cyclic adenosine monophosphate (Gs-cAMP) signalling pathway results in bronchodilation and relief of asthma symptoms. However β 2-agonists may also activate non canonical (Gs-cAMP independent) β -arrestin mediated pro-inflammatory signalling pathways via extracellular signal regulated kinases (ERK1/2)¹. In knockout mice β -arrestin-2 regulates the development of allergic asthma². Chronic exposure to LABA causes adaptive down-regulation and uncoupling of β 2ADR with associated sub-sensitivity of response and in some cases worse asthma control³. In the antigen driven mouse model, depletion of adrenaline the natural ligand for the β 2ADR, prevented the development of asthma⁴. Replacement of β 2ADR signalling by administration of formoterol (LABA) restored the asthma phenotype, showing that agonist induced activation of β 2ADR results in development of asthma⁴. This suggests paradoxically that perhaps using an inverse agonist might be a better strategy in asthma management. An inverse agonist is one which stabilises the inactive receptor conformation and blocks its constitutive activity, by switching off β 2ADR signalling.

β -antagonists are contra-indicated in patients with asthma even using β 1 selective agents, due to the effects of β 2ADR blockade by promoting cholinergic transmission and bronchoconstriction, especially upon first dose exposure. It would therefore seem counterintuitive to ever consider giving a non selective β -blocker such as nadolol as anti-asthma therapy.

It has been proposed that switching off β 2ADR (thereby lowering cAMP) with an inverse β 2-agonist such as nadolol might paradoxically result in improved

in airway AHR and associated control⁵. This concept was supported by data from knockout mice devoid of β 2ADR who when exposed to antigen did not develop airway hyper-responsiveness (AHR) or other cardinal inflammatory features of the asthma phenotype, while the same phenomenon also occurred with nadolol treatment in wild type mice expressing β 2ADR⁶. Moreover nadolol confers complimentary corticosteroid sparing anti-inflammatory activity in the mouse model⁷.

It was subsequently shown in adrenaline depleted mice that beneficial effect of β -blockers may be ligand specific in that exposure to propranolol but not nadolol resulted in the development of the asthma phenotype, while in wild type mice nadolol but not propranolol prevented the occurrence of asthma⁸.

Thus nadolol reduces cAMP as a canonical inverse agonist and is a non canonical neutral antagonist on ERK1/2¹, resulting in an overall anti-asthmatic profile. Propranolol acts as a so called biased ligand, stimulating ERK1/2 as a non canonical partial agonist while reducing cAMP as a canonical inverse agonist, resulting in a net null or pro-asthmatic profile^{1,8} (Figure).

Studies in humans have revealed conflicting results with oral non selective β -blockers. Two open label studies with nadolol (10-40mg/day) in inhaled corticosteroid (ICS) naïve intermittent asthma showed improvements in methacholine AHR^{9,10}. One could cogently argue that using nadolol as monotherapy without ICS is not clinically relevant, in the same way that one would never give a LABA without ICS. In contrast two placebo controlled trials with propranolol (20-80mg/day) in ICS treated persistent asthma showed no improvement in methacholine or histamine AHR or in other inflammatory markers^{11,12}. Furthermore the salutary effect of an increased ICS dose

confirmed that there was further room for potential improvement with propranolol and no corticosteroid sparing activity¹². It is possible that the impact of concomitant ICS might have either nullified the effect of propranolol due to β 2ADR up-regulation, or perhaps counteracted a putative pro-inflammatory action of propranolol.

In both of these studies^{11,12} there was a non significant 2-4% fall in pre-challenge FEV1 after propranolol versus placebo, while reliever use, asthma control and quality of life were not significantly affected. The effect of sequential nebulised salbutamol and ipratropium after challenge showed a significant 5% attenuation in FEV1 between propranolol and placebo, although full recovery back to baseline occurred by 30 minutes. Hence it may be possible to overcome the competitive antagonism due to propranolol by using a higher dose of β 2-agonist. During initial propranolol dose titration, concomitant tiotropium prevented bronchoconstriction due to increased cholinergic transmission¹³. Post hoc analysis showed that propranolol induced bronchoconstriction was greater in patients who expressed the arginine-16 β 2ADR polymorphism¹⁴.

A placebo controlled trial (ClinTrials.gov identifier:NCT 01804218) evaluating oral nadolol as monotherapy in mild ICS naïve asthma will complete in 2016. Assuming it shows attenuation of methacholine AHR, it would also need to exhibit anti-inflammatory activity comparable to low dose ICS. An inhaled formulation of nadolol in development (Invion Ltd, Brisbane, Australia) might offer a superior therapeutic ratio as a consequence of higher lung levels along with lower systemic exposure due to its hydrophilicity.

If it transpires that switching off β 2ADR confers improvements in persistent asthma, then it will surely challenge current dogma and guidelines regarding continuous β 2ADR stimulation with LABA. The concept of moving therapy from β -agonists to their antagonists has already been adopted by cardiologists in heart failure. Perhaps it is now the turn of pulmonologists to start thinking along similar lines for the treatment of asthma.

References

1. van der Westhuizen ET, Breton B, Christopoulos A, Bouvier M. Quantification of ligand bias for clinically relevant beta2-adrenergic receptor ligands: implications for drug taxonomy. *Mol Pharmacol* 2014; **85**(3): 492-509.
2. Walker JK, Fong AM, Lawson BL, et al. Beta-arrestin-2 regulates the development of allergic asthma. *J Clin Invest* 2003; **112**(4): 566-74.
3. Grove A, Lipworth BJ. Bronchodilator subsensitivity to salbutamol after twice daily salmeterol in asthmatic patients. *Lancet* 1995; **346**(8969): 201-6.
4. Thanawala VJ, Forkuo GS, Al-Sawalha N, et al. beta2-Adrenoceptor agonists are required for development of the asthma phenotype in a murine model. *Am J Respir Cell Mol Biol* 2013; **48**(2): 220-9.
5. Lipworth BJ, Williamson PA. Beta blockers for asthma: a double-edged sword. *Lancet* 2009; **373**(9658): 104-5.
6. Nguyen LP, Lin R, Parra S, et al. Beta2-adrenoceptor signaling is required for the development of an asthma phenotype in a murine model. *Proc Natl Acad Sci U S A* 2009; **106**(7): 2435-40.
7. Nguyen LP, Singh B, Okulate AA, et al. Complementary anti-inflammatory effects of a beta-blocker and a corticosteroid in an asthma model. *Naunyn Schmiedebergs Arch Pharmacol* 2012; **385**(2): 203-10.
8. Thanawala VJ, Valdez DJ, Joshi R, et al. beta-Blockers have differential effects on the murine asthma phenotype. *Br J Pharmacol* 2015; **172**(20): 4833-46.
9. Hanania NA, Singh S, El-Wali R, et al. The safety and effects of the beta-blocker, nadolol, in mild asthma: an open-label pilot study. *Pulm Pharmacol Ther* 2008; **21**(1): 134-41.

10. Hanania NA, Mannava B, Franklin AE, et al. Response to salbutamol in patients with mild asthma treated with nadolol. *Eur Respir J* 2010; **36**(4): 963-5.
11. Short PM, Williamson PA, Anderson WJ, Lipworth BJ. Randomized placebo-controlled trial to evaluate chronic dosing effects of propranolol in asthma. *Am J Respir Crit Care Med* 2013; **187**(12): 1308-14.
12. Anderson WJ, Short PM, Williamson PA, Manoharan A, Lipworth BJ. The inverse agonist propranolol confers no corticosteroid-sparing activity in mild-to-moderate persistent asthma. *Clin Sci (Lond)* 2014; **127**(11): 635-43.
13. Short PM, Anderson WJ, Williamson PA, Lipworth BJ. Effects of intravenous and oral beta-blockade in persistent asthmatics controlled on inhaled corticosteroids. *Heart* 2014; **100**(3): 219-23.
14. Anderson WJ, Short PM, Manoharan A, Lipworth JL, Lipworth BJ. Influence of beta2-adrenoceptor 16 genotype on propranolol-induced bronchoconstriction in patients with persistent asthma. *Ann Allergy Asthma Immunol* 2014; **112**(5): 475-6.

Figure Legend

Effects of β -blockers on canonical (Gs-cAMP) and non-canonical signalling (ERK1/2). Nadolol acts as an inverse agonist (solid arrow) reducing cAMP and a neutral antagonist (dashed arrow) on ERK1/2. Propranolol acts as an inverse agonist (solid arrow) to reduce cAMP and as a partial agonist (dotted arrow) to stimulate ERK1/.

Figure

