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

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Declaration of interests

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Stimulation of airway β2-adrenoceptors (β2ADR) 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 β2-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 asthma[2]. Chronic exposure to LABA causes adaptive down-regulation and uncoupling of β2ADR with associated sub-sensitivity of response and in some cases worse asthma control[3] . In the antigen driven mouse model, depletion of adrenaline the natural ligand for the β2ADR, prevented the development of asthma[4]. Replacement of β2ADR signalling by administration of formoterol (LABA) restored the asthma phenotype, showing that agonist induced activation of β2ADR results in development of asthma[4]. 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 β2ADR signalling.

β-antagonists are contra-indicated in patients with asthma even using β1 selective agents, due to the effects of β2ADR 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 β2ADR (thereby lowering cAMP) with an inverse β2-agonist such as nadolol might paradoxically result in improved

in airway AHR and associated control[5]. This concept was supported by data from knockout mice devoid of β2ADR 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 β2ADR[6]. Moreover nadolol confers complimentary corticosteroid sparing anti-inflammatory activity in the mouse model[7].

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 asthma[8]. Thus nadolol reduces cAMP as a canonical inverse agonist and is a non canonical neutral antagonist on ERK1/2[1], 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 activity[12]. It is possible that the impact of concomitant ICS might have either nullified the effect of propranolol due to β2ADR 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 verses 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 β2-agonist. During initial propranolol dose titration, concomitant tiotropium prevented bronchoconstriction due to increased cholinergic transmission[13]. Post hoc analysis showed that propranolol induced bronchoconstriction was greater in patients who expressed the arginine-16 β2ADR polymorphism[14].

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 β2ADR confers improvements in persistent asthma, then it will surely challenge current dogma and guidelines regarding continuous β2ADR 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.

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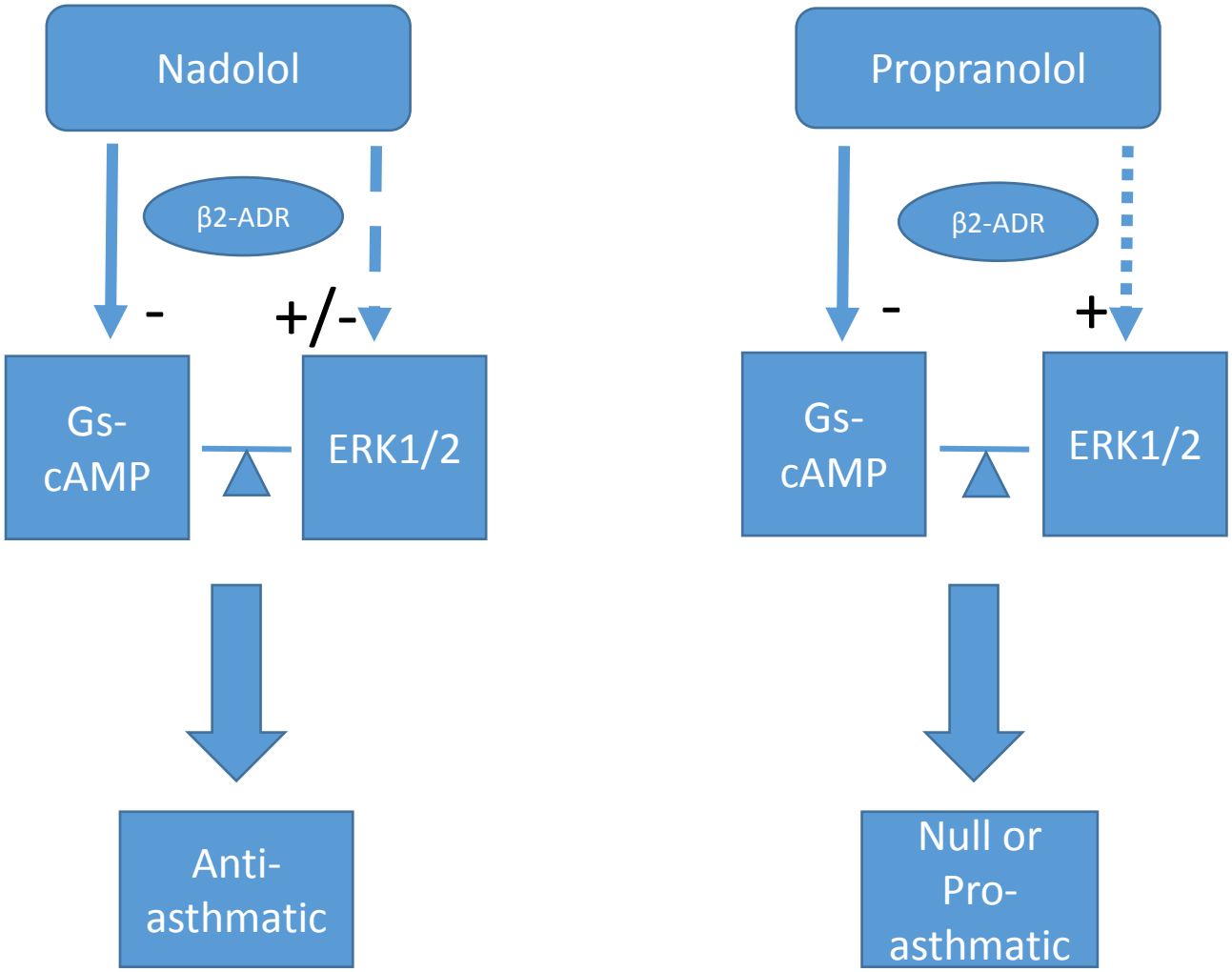
Figure Legend

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


Nadolol
β2-ADR
-
+/-
Gs-
cAMP
ERK1/2
Anti-
asthmatic
Propranolol
β2-ADR
-
+
Gs-
cAMP
ERK1/2
Null or
Pro-
asthmatic