HYPOTHESIS

Think the impossible: $\beta$-blockers for treating asthma

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ABSTRACT

Asthma was originally thought to be associated with an intrinsic defect in $\beta_2$ADR ($\beta_2$-adrenoceptor) function, tipping the balance towards parasympathetic bronchoconstriction. Hence $\beta$-blocking drugs (such as $\beta_2$ADR antagonists and inverse agonists) may cause acute bronchoconstriction which, in turn, may be attenuated by anti-cholinergic agents. Although $\beta_2$-agonists are highly effective for the acute relief of bronchoconstriction, their chronic use is accompanied by an adaptive reduction in $\beta_2$ADR numbers and associated desensitization of response, resulting in increased exacerbations and rare cases of death. The hypothesis examined in the present article is that, while single dosing with a $\beta$-blocker may cause acute bronchoconstriction, chronic dosing may afford putative beneficial effects including attenuated airway hyper-responsiveness.

INTRODUCTION

Regulation of human airway smooth muscle is dependent on complex interactions between inflammatory and neurological processes. Neurological control is a balance between sympathetic and parasympathetic activity, which causes relaxation and constriction respectively. Indeed, historically it was proposed that asthma may be caused by an intrinsic defect in $\beta_2$ADRs ($\beta_2$-adrenoceptors), which allowed parasympathetic (bronchoconstrictor) tone to dominate. As medical students we are taught that $\beta$-blockers ($\beta_2$ADR antagonists) should never be given to asthmatic patients because of the potential to induce life-threatening acute bronchoconstriction due to unopposed cholinergic stimulation. Similarly, the use of both short- and long-acting $\beta_2$-agonists ($\beta_2$ADR agonists) as first line bronchodilator therapy is well established in management guidelines [1]. Thus to even propose a hypothesis that $\beta$-blockers could be used to treat asthma would be anathema to most clinicians.

$\beta$-AGONISTS AND -ANTAGONISTS

There is now increasing evidence to suggest that while long-acting $\beta_2$-agonists may produce improvements in symptoms and lung function [i.e. FEV$_1$ (forced expiratory volume in 1 s) and peak flow], their long-term use may be associated with paradoxical worsening of asthma control in terms of exacerbations (and rare cases of death), despite concomitant inhaled corticosteroid therapy [2–5]. This is perhaps not surprising given that a reduction in $\beta_2$ADR number and desensitization of response occurs as a predictable adaptation to regular exposure to long-acting $\beta_2$-agonists even when co-administered with inhaled corticosteroids [6]. There is now evidence to show that susceptible individuals with the $\beta_2$ADR homozygous Arg16 genotype may fare worse after chronic dosing with long-acting $\beta_2$-agonists, particularly with regard to bronchoprotective effects and exacerbations [7,8]. Interestingly, this same genotype also predicts worse survival for patients receiving $\beta$-blockers after acute coronary syndrome [9].

Key words: adrenoceptor, airway hyper-responsiveness, asthma, $\beta$–blocker, bronchoconstriction, heart failure, smooth muscle.

Abbreviations: ADR, adrenoceptor; AHR, airway hyper-responsiveness; FEV$_1$, forced expiratory volume in 1 s.

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$\beta$-Blockers are indicated for a variety of conditions including hypertension, ischaemic heart disease, heart failure, migraine and anxiety. However, they remain contraindicated for patients with concomitant asthma due to the risk of acute bronchoconstriction. Bronchoconstriction is worse following administration of $\beta$-blockers which block both $\beta_1$ ADR and $\beta_2$ ADR subtypes (so called ‘non-selective’ drugs such as propranolol or nadolol) compared with ‘cardioselective’ drugs which exhibit less $\beta_2$ ADR blockade (such as bisoprolol, betaxolol, atenolol or metoprolol) [10]. A previous meta-analysis has shown that, whilst single dosing with cardioselective drugs produces significant falls in FEV$_1$, chronic dosing does not cause a significant reduction in FEV$_1$ or an impaired response to salbutamol [11]. The mechanism of $\beta$-blocker-induced bronchoconstriction is poorly understood, but it is of interest that anti-cholinergic drugs can prevent its occurrence, possibly due to cross-talk between $\beta_2$ ADRs and muscarinic M$_2$ autoreceptors [12] (Figure 1A).

The $\beta_2$ ADR is a GPCR (G-protein-coupled receptor). It is now recognized that a subset of $\beta$-blockers not only bind to $\beta_2$ ADRs preventing agonist binding (neutral antagonists), but also reverse the constitutive unliganded activity of the receptors (inverse agonist). These ‘inverse agonists’ (which include nadolol, ciproxolol, bisoprolol and metoprolol) have been reported to have actions beyond traditional antagonists, including inactivation of unbound ADRs and intracellular signalling via...
messengers other than G-proteins. Indeed some believe it is these inverse agonist properties which may be crucial to the success of certain β-blockers in heart failure [13].

THE HEART FAILURE PARADOX AND ASTHMA

It was previously considered that β-agonists would be beneficial for treating heart failure because they produce acute improvements in myocardial contractility and cardiac output. However, chronic dosing was associated with adaptive β-ADR down-regulation and desensitization of response, along with increased mortality. Until recently, β-blockers were contraindicated in heart failure because acute dosing reduced myocardial contractility, which was a risk for acute decompensated pulmonary oedema. It was subsequently discovered that chronic dosing produced beneficial effects on both ejection fraction and mortality. As a result, gradual introduction and titration of β-blockers is now considered standard therapy in management guidelines [14,15]. The paradox between effects of acute and chronic β-blockade in heart failure prompted some researchers to re-examine the role of β2-ADR antagonism in asthma [16] and to question whether there may be a double-edged sword, i.e. a disconnect between the beneficial effects of chronic dosing and the detrimental effects acutely (Table 1). This is all the more plausible when it is considered that chronic exposure to β2-agonists causes β2-ADR down-regulation in association with worsening asthma control, whereas chronic administration of β-blockers causes receptor up-regulation.

MURINE AND HUMAN MODELS

The first evidence in support of this hypothesis was derived from studies using the ovalbumin-sensitized mouse model of asthma. It was shown that acute dosing with metoprolol or nadolol produced bronchoconstriction, whereas chronic dosing produced bronchodoprotection against methacholine challenge [a cholinergic spasmogen which induces AHR (airway hyper-responsiveness)] [17–19]. This beneficial effect was observed in conjunction with reduced inflammation and mucous metaplasia, and simultaneous up-regulation of β2-ADRs. These effects were more marked with nadolol than metoprolol, but were also observed with the highly selective β2-agonist ICI 118,551, suggesting that the effects are mediated via β2-ADRs. Given that metoprolol (a selective β1-agonist) conferred bronchoprotection and β2-ADR up-regulation, one might conclude that a relatively small degree of β2-blockade might be sufficient to confer benefits. Further evidence to support the potential role of β-blockers comes from β2-ADR-knockout mice who, being devoid of such receptors, do not develop the asthmatic phenotype in response to allergen stimulation [20].

Inspired by these murine models, Hanania et al. [21] have now completed the first open-label study in mild corticosteroid-naïve asthmatics using a 9 week incremental dosing protocol of nadolol (10–40 mg) [21]. As anticipated, there was a fall in FEV1 after the first dose. After chronic dosing, the FEV1 was statistically significantly lower than at baseline (5 %), but this change was asymptomatic and accompanied by a significant improvement in AHR to methacholine challenge, amounting to a 1.8 doubling-dilution shift in the PC20 (dose causing a 20 % fall in FEV1) value. To put this into a clinical context, a 1–2 doubling-dilution shift is the same order of magnitude that one observes with inhaled corticosteroids and an associated reduction in exacerbations. It would appear, therefore, that if one can tolerate the initial acute deterioration in lung function on first exposure with β-blockers, there would be a small residual degree of impairment in airway calibre after chronic dosing, but at the same time a significant improvement in AHR (Figures 1B and 1C). This disconnect between worsening resting airway tone and improved AHR is intriguing because one would normally expect the latter to worsen when airway calibre becomes narrower, whereas the opposite was found by Hanania et al. [21]. This disconnect is not unique to β2-blockade, however, as chronic dosing with β-agonists mirrors this in some patients by reducing resting tone and increasing AHR. This suggests that neurological control of the airway is more complex than commonly supposed with important receptor actions pre-junctionally as well as on the smooth muscle itself. The potential role of the pre-junctional M2 receptor in the pathogenesis of asthma has been

Table 1  β-ADRs: acute compared with chronic therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Heart failure</th>
<th>Asthma</th>
<th>β-ADR expression</th>
</tr>
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<tbody>
<tr>
<td>Acute</td>
<td>Agonist Beneficial (↑ contractility)</td>
<td>Beneficial (bronchodilatation)</td>
<td>↔</td>
</tr>
<tr>
<td></td>
<td>Antagonist Detrimental (↓ contractility)</td>
<td>Detrimental (bronchoconstriction)</td>
<td>↔</td>
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<tr>
<td>Chronic</td>
<td>Agonist Detrimental (↑ mortality)</td>
<td>Detrimental! (↑ AHR/Exac)</td>
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</tr>
<tr>
<td></td>
<td>Antagonist Beneficial (↓ mortality)</td>
<td>Beneficial! (↓ AHR)</td>
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suggested before, supported by observation that viruses and eosinophils can suppress M<sub>2</sub> function (hence reducing its inhibitory effects on acetylcholine release causing increased AHR) [12]. It is equally plausible to suppose that β<sub>2</sub>ADR may have important regulatory roles in their pre-junctional expression, rather than simply smooth muscle targets to oppose anti-cholinergic bronchoconstriction.

FURTHER HUMAN STUDIES

This begs the question as to what further studies are required to test the hypothesis that β-blockers may be beneficial for asthma. First, the findings of Hanania et al. [21] with nadolol need to be replicated using a double-blind placebo-controlled design. It would also be important to know whether the improvements in AHR were confined to methacholine challenge or applicable to other stimuli, such as histamine or AMP, which do not act via the smooth muscle cholinergic pathway (Figure 1). It would be relevant to look at inflammatory surrogates, such as exhaled breath condensate and induced sputum for eosinophils and cytokines, given the anti-inflammatory benefits observed in mouse models.

It will also be important to compare efficacy and tolerability of cardioselective and non-selective β-blockers to establish their relative ability to improve AHR whilst minimizing acute falls in baseline FEV<sub>1</sub>. If the beneficial properties observed are related to receptor up-regulation, it is likely that the degree of β<sub>2</sub>ADR antagonism (and perhaps inverse agonism) determines its efficacy. However, it may be possible that a drug such as metoprolol is a suitable compromise in possessing enough β<sub>2</sub>-blockade to be effective without inducing too much initial bronchoconstriction. For example, the β<sub>1</sub>ADR/β<sub>2</sub>ADR selectivity ratio for metoprolol is 2.3 compared with 13.5 for bisoprolol and 0.043 for nadolol; i.e. metoprolol has a 2.3-fold greater affinity for β<sub>1</sub>ADR than β<sub>2</sub>ADR [22]. Cardioselective β-blockers such as celiprolol also exhibit partial β<sub>1</sub>-agonist activities. As such, whilst they will not cause acute bronchoconstriction, they can cause β<sub>2</sub>ADR down-regulation through their agonist activity and, hence, be unsuitable as an asthma treatment.

Given that the study by Hanania et al. [21] used corticosteroid-naïve asthmatics, another important consideration is whether the use of concomitant inhaled corticosteroids will affect potential benefits or risks of β-blockers. As long-acting β<sub>2</sub>-agonists are only used as add-on therapy to inhaled corticosteroids, one could argue that this would also apply to β-blockers. It could be argued that the risk of exacerbation on β-blockers alone would be much greater without the protective anti-inflammatory effect of inhaled steroid therapy. In this regard, it has been shown that 2000 μg/day of inhaled fluticasone has no effect on ex vivo lymphocyte β<sub>2</sub>ADR function in asthmatics, suggesting that even high dose inhaled steroids would not interfere with β-blocker-induced β<sub>2</sub>ADR up-regulation, hence it is plausible that the two drugs could (and should) be used concomitantly [23].

Patient selection for initial challenge-based proof-of-concept studies will be crucial in terms of ensuring that eligible individuals have stable asthma control parameters, but still have marked enough AHR to have potential room for improvement. Ensuring patients have minimal peak flow diurnal variability and minimal β<sub>2</sub>-agonist rescue requirements will be paramount for safety purposes at screening. Moreover, any regular use of short- or long-acting β<sub>2</sub>-agonists would have potential confounding effects on β<sub>2</sub>ADR regulation. In other words, agonist promoted down-regulation could conceivably mask any up-regulation due to β-blockers.

SAFETY CONCERNS

There are two main safety concerns in such trials. First, the risk of precipitating profound acute bronchoconstriction during the initial induction phase of β-blockers, and secondly, which reliever drug to use to reverse acute bronchoconstriction in the presence of prolonged β<sub>2</sub>ADR occupancy. Previous studies with a single dose of nadolol have shown that even a 5 mg dose produces complete attenuation of β<sub>2</sub>ADR-mediated responses to intravenous salbutamol or exercise-induced hyperkalaemia, similar to an 80 mg dose of nadolol [24]. Unsurprisingly, the 5 mg dose of nadolol was associated with significantly less β<sub>1</sub>-blockade of exercise heart rate response. Taken together, these findings suggest that such a low dose of nadolol might be suitable for maintenance treatment in asthmatics, as it would produce sufficient β<sub>2</sub>ADR up-regulation while at the same time being tolerable in terms of adverse cardiovascular effects, such as bradycardia and postural hypotension; i.e. a 5 mg dose exhibits a high β<sub>1</sub>ADR/β<sub>2</sub>ADR selectivity ratio. However, the findings by Hanania et al. [21] reveal that the benefit on AHR is dose-related, with only the 20 and 40 mg doses producing a significant improvement in PC<sub>20</sub>. One of the lessons to be learnt from heart failure is that gradual dose escalation with β-blockers improves cardiovascular tolerability during the initiation phase; however, this improved tolerability for adverse cardiovascular effects may be predominantly due to dose-related β<sub>1</sub>-blockade [25]. As nadolol at a putative starting dose of 5 mg has a similar degree of β<sub>2</sub>-blockade compared with 80 mg, one might anticipate a risk of acute bronchoconstriction even at such a low starting dose.

The issue of the acute bronchoconstrictor response after the initial exposure could be obviated by
pre-treatment with an anti-cholinergic agent. It would appear prudent to pre-treat and maintain with a long-acting \( M_2 \)-selective anti-cholinergic agent, such as tiotropium, for the duration of \( \beta_2 \)-blocker exposure (Figure 1D). In the absence of tiotropium cover, another possibility would be to use a short-acting non-selective (\( M_2/M_3 \)) anti-cholinergic agent, such as ipratropium, for on-demand rescue therapy. One would anticipate that, in the presence of \( \beta_2 \)ADR occupancy by nadolol, salbutamol would be ineffective as acute reliever therapy. It has been shown that the response to intravenous isoprenaline is blocked to a similar degree when comparing the single and chronic dosing effects of 40 mg of nadolol after 2 weeks [10]. However, it has also been shown that, although the isoprenaline-induced lymphocyte cAMP response is blunted after 2 weeks of propranolol or timolol, there is restoration of response back to pre-treatment baseline levels after 4 weeks of treatment [26,27]. This suggests that \( \beta_2 \)ADR up-regulation occurs between 2–4 weeks of treatment with \( \beta_2 \)-blockers. Hence, until the \( \beta_2 \)ADRs have up-regulated, the acute reliever response to salbutamol would be blunted and alternative acute bronchodilator strategies would be required, such as ipratropium, aminophylline or magnesium, which act through different pathways on airway smooth muscle.

Acute exposure to high dose intravenous corticosteroid has been shown to rapidly supra-normalize lymphocyte \( \beta_2 \)ADR numbers and the associated cAMP response in asthmatics [28], such that its acute administration might be a useful strategy to restore \( \beta_2 \)ADR responsiveness in the first 2 weeks of \( \beta_2 \)-blocker treatment; i.e. high dose intravenous corticosteroid could restore the response to high dose salbutamol in the vulnerable period before \( \beta_2 \)-blocker-induced up-regulation has occurred. Clearly studies looking at these various acute rescue strategies would be required after a single first dose exposure to nadolol, possibly including a bronchial challenge, to simulate the worse case scenario of an episode of acute bronchoconstriction in a \( \beta_2 \)-blocked asthmatic.

Another possibility is to give an initial test dose of intravenous esmolol, a fast-acting short-duration cardio-selective \( \beta_2 \)-blocker, in order to screen out asthmatics susceptible to profound bronchoconstriction due to even a small degree of \( \beta_2 \)-blockade. However, patients who tolerate a test dose of esmolol may still not tolerate the first dose exposure to a non-selective agent such as nadolol. When escalating the dose of nadolol during the initial induction phase, a further limiting factor will be dose-related \( \beta_2 \)-blockade producing bradycardia and postural hypotension. This particular problem could be obviated by the development of either an inhaled formulation of a non-selective \( \beta_2 \)-blocker or an orally active \( \beta_2 \)-selective antagonist such as ICI 118,551. \( \beta_2 \)ADR genotype testing may also prove useful to screen out individuals most susceptible to profound first dose bronchoconstriction.

### THE WAY FORWARD

If further proof-of-concept studies confirm preliminary animal and human findings, one might ask where this research might lead. The next step would be the hardest and bravest pill to swallow: challenging equipoise among opinion leaders and attempting to recruit into multi-centre studies examining long-term efficacy and safety, focussing on exacerbations as the primary outcome. It would be particularly challenging to initiate such studies given the established position in management guidelines of long-acting \( \beta_2 \)-agonists, which are increasingly used in combination with inhaled corticosteroid in a single inhaler. Safety must always be the main concern in developing new treatment strategies (as it once was with heart failure), but this should not deter us from challenging dogma when there is sound scientific reason to do so.

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