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β-Adrenoceptor Inverse Agonists in Asthma

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Abstract

β₂-adrenoceptor agonists are very effective bronchodilators and play a major role in every stage of asthma management. However, their chronic, regular use is associated with detrimental effects including an increase in asthma-related deaths. Conversely, recent data suggest that certain β-blockers, specifically β-adrenoceptor inverse agonists, may be useful in the chronic treatment of asthma. Here we review the data for this observation and the signaling pathways that may be involved. The data suggest that β₂-adrenoceptor signaling is required to produce maximal airway inflammation and hyperresponsiveness, and the signaling pathway responsible for these effects is likely the non-canonical β-arrestin-2 pathway. Therefore, β-adrenoceptor inverse agonists may produce their beneficial chronic effects by inhibiting constitutive or ligand-induced activation of this pathway. Both lung parenchymal and hematopoietic cells appear to be involved in mediating the beneficial effects of β-adrenoceptor inverse agonists.

Keywords

asthma; β-adrenoceptor agonist; airway inflammation; β-blocker; β-adrenoceptor inverse agonist

Introduction

In 1997, the U.S. Food and Drug Administration (FDA) approved a β-blocker, carvedilol, for the treatment of congestive heart failure (CHF). This completed a remarkable turnaround that began when Fynn Waagstein and colleagues published the first positive results using a β-blocker to treat CHF in 1975 [1]. To our knowledge, this marked the first time that a drug moved from being contraindicated to being a drug of choice in the disease where it was once contraindicated [2,3].

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CHF is a disease of impaired cardiac output, and logic indicated what was needed in its treatment were β -adrenoceptor (β -AR) agonists to increase contractility, not β -blockers (β -AR antagonists and inverse agonists) which are negative inotropic agents. However, the results of trials using β -AR agonists showed that while these did initially increase cardiac contractility and improve the hemodynamics of CHF, their chronic use was associated with increased mortality [4,5]. This phenomenon of a complete reversal in the effects of drugs dependent upon the duration of treatment prompted one of us to inquire whether this was a unique feature of CHF, or if it was a more general principle [6]. This started our research into the chronic use of β -blockers for the treatment of asthma.

In asthma, β -AR agonists, specifically agonists of the β_2 -AR subtype, are potent bronchodilators that are essential tools at every step in the management of asthma. These drugs are very useful during an acute asthma attack where they provide effective and rapid relief of symptoms. However, some studies suggested that the chronic use of β_2 -AR agonists was associated with an increased incidence of adverse effects, including increased asthma-related mortality [7,8]. Perhaps the best example is the randomized, double-blind, placebo-controlled SMART study. In this large study of over 26,000 patients, chronic treatment with salmeterol resulted in an increase in respiratory-related deaths [7].

Thus, while asthma and CHF are unrelated in their clinical presentation and in many other aspects, from a receptor point of view, the diseases appear related. In both diseases the acute use of β -AR agonists results in improvement of symptoms in the disease, while their chronic use can result in an increase in mortality. Likewise, in both diseases, β -blockers were originally contraindicated, while now, at least in CHF, certain β -blockers are used as first-line treatment. However, in both CHF, and in a murine asthma model, not all β -blockers are equally effective. In CHF, bucindolol and celiprolol, β -blockers with β_2 -AR partial agonist properties [9,10], have not produced a decrease in mortality [11,12]. Similarly, in a murine asthma model, alprenolol, another β -blocker with weak β_2 -AR agonist properties [13], also failed to show any beneficial effect [13,14••].

β -AR inverse agonists; a subset of β -blockers

In the 1990's, evidence began to emerge that G protein-coupled receptors (GPCRs) could exist in a spontaneously or constitutively active state which was capable of signaling in the absence of any agonist binding [15–18]. Simultaneous with this discovery of signaling by unliganded or empty receptors was the discovery that certain, but not all, antagonists for GPCRs could also inactivate these spontaneously active receptors. This subset of 'blockers' was termed inverse agonists to differentiate them from antagonists (for further differentiation; a pure neutral antagonist has no partial or inverse agonist activity). Thus, while both inverse agonists and antagonists block agonist-induced activation of the receptor, only the former could turn off the empty active receptors [17]. Whereas prior to this discovery all antagonists were assigned zero efficacy, the ability of inverse agonists to turn off the 'basal' signaling by empty receptors to various degrees forced efficacy values for drugs into negative values (Figure 1). While the evidence consists of small numbers of studies, in both isolated myocytes from human failing hearts [10] and in murine models of asthma [13,14,19•], it appears that it is only β -AR inverse agonists that provide a beneficial effect with chronic administration in CHF and these asthma models.

β -adrenoceptor inverse agonist treatment in mouse models of asthma

The possibility that the acute beneficial effects of β_2 -AR agonists and detrimental effects of β_2 -AR inverse agonists might be mirrored by chronic beneficial effects of β_2 -AR inverse agonists in addition to the established chronic detrimental effects of β_2 -AR agonists was tested in a mouse model of allergic asthma in 2004 [13]. As expected for the acute effects, the β_2 -AR

agonist albuterol attenuated and the β_2 -AR inverse agonist nadolol aggravated airway hyperresponsiveness when administered by intravenous bolus 15 minutes before intravenous methacholine infusion. However, after 28 days of continuous drug administration by minipump or in food, the protective effect of albuterol was lost whereas nadolol gained a protective effect against methacholine-induced airway hyperresponsiveness. Similar inversions were observed between the acute and chronic effects of the weak β_2 -AR agonist alprenolol and the β_2 -AR inverse agonist carvedilol, suggesting that these represent class effects of inverse agonists rather than responses to specific ligands. This study did not identify a mechanism for the attenuation of airway hyperresponsiveness by chronic administration of a β_2 -AR inverse agonist, but clearly demonstrated the phenomenon for the first time.

To evaluate possible mechanisms of the beneficial effects of chronic administration of β_2 -AR inverse agonists, lung inflammation and airway epithelial mucin production, two cardinal features of the asthma phenotype, were examined [19•]. Administration of nadolol in the diet for 28 days reduced eosinophils in the bronchoalveolar lavage fluid by 73% and mucin production by 86%. Similar results were obtained with administration of the β_2 -AR selective inverse agonist ICI-118,551 by osmotic minipump for 28 days. Remarkably, neither inverse agonist was fully effective when administered for only 7 days. Treatment with a β_2 -AR inverse agonist was required during antigen challenge but not during antigen sensitization to achieve a beneficial effect [19•].

These studies did not directly address the cell type(s) on which β_2 -AR inverse agonists act; however, the profound effect on mucin production suggested that at least some of the response is due to direct effects on airway epithelial cells since a partial reduction in an upstream signal often does not result in a commensurate reduction in a downstream effect. Indeed, it is possible that the reduction in inflammation is due in part to reduced parenchymal cell release of chemokines as identified in the β -arrestin-2 knockout mouse [20] (see below). β_2 -ARs are highly expressed in airway epithelial cells [21], and their activation promotes chloride release by activation of cystic fibrosis transmembrane conductance regulator (CFTR) that leads to increased airway luminal liquid [22,23] and increased ciliary beat frequency [24]. Leukocyte secretory granules contain catecholamines [25], so their release during infection might promote microbial clearance by increasing mucin production, liquid release, and ciliary beat frequency to augment mucociliary clearance.

Required signaling versus biased agonism

Studies using β_2 -AR inverse agonists to modulate the asthma phenotype do not distinguish whether their effects are due to the blockade of constitutive signaling from β_2 -AR or to biased agonism (the ability of a synthetic ligand to preferentially activate non-canonical signaling at a receptor capable of signaling through multiple pathways). The β_2 -AR has a substantial level of constitutive activity, thus making the first possibility plausible. However, biased agonism has been suggested to play a role in the beneficial chronic effects of the β -AR inverse agonist carvedilol in the myocardial function of CHF patients [26•], making the second possibility also plausible. To discriminate between these possibilities, the effect of genetic deletion of the β_2 -AR in a mouse model of asthma was analyzed [14••]. The knockout essentially phenocopied the chronic administration of a β_2 -AR inverse agonist, showing a marked attenuation of airway hyperresponsiveness, inflammation, and mucin production. This result supports the interpretation that the beneficial effects of the chronic use of β_2 -AR inverse agonists in asthma is due to a reduction in required signaling from the β_2 -AR for full expression of the asthma phenotype rather than to biased agonism. Whether constitutive signaling from empty β_2 -AR is sufficient to fully support the development of the asthma phenotype or whether activation of β_2 -AR by endogenous catecholamines from neurons or leukocytes is required is not yet known with certainty. The lack of effect of alprenolol [14••], a β -blocker with weak β_2 -AR

agonist properties in some systems, at reducing the development of the asthma phenotype suggests that endogenous ligands are not required since partial agonists act as blockers in the presence of strong agonists such as the endogenous ligand epinephrine (see above). However, the weak β_2 -AR agonist properties observed in some systems [13,27], could be sufficient to support the inflammatory response, so this result cannot be viewed as definitive.

Non-canonical signaling from the β_2 -adrenoceptor

Clues to the signaling pathway downstream of the β_2 -AR that is required for full expression of the asthma phenotype come from the protection provided by genetic deletion of β -arrestin-2. Mice lacking β -arrestin-2 demonstrate marked attenuation of the classic features of the asthma phenotype despite the appearance of serum allergen-specific immunoglobulins [20]. This indicates that the non-canonical signal transduction property of β -arrestin-2, rather than its G protein signal quenching ability, underlies this effect. We propose that the β_2 -AR constitutive or agonist-activated signaling required for the development of the asthma phenotype occurs via a β -arrestin-dependent pathway. However, it is currently unknown in which cell type β_2 -AR signaling is required for asthma phenotype development.

Lung-infiltrating Th2-differentiated CD4⁺ T cells exert a crucial role in the initiation and perpetuation of the asthma phenotype through effects on airway epithelial and smooth muscle cells [28]. Besides being targets for T cells, these lung structural cells are also a source of pro-inflammatory mediators that actively perpetuate the asthma phenotype [29,30]. β -arrestin-2 expression by both hematopoietic and non-hematopoietic cells has been shown to be required for full development of the asthma phenotype [31••]. Thus, β -arrestin-2-mediated regulation of at least one immune and one lung structural cell type is involved.

T cells express functional β_2 -ARs that mediate, among other functions, Th2 cell pro-survival signals [32]. Although β -arrestin-2-mediated signal transduction of this effect may contribute to the development of the asthma phenotype, the observation that β -arrestin-2-KO mice display a more dramatic protection from the development of asthma than β_2 -AR-KOs or mice chronically treated with β_2 -AR inverse agonists suggests that β -arrestin-2-mediated signal transduction from not only β_2 -ARs, but also from additional seven-transmembrane receptors, is involved in the development of allergic asthma. Evidence shows that normal allergen-induced T cell migration to the lung requires β -arrestin-2 and we propose chemokine receptor-induced β -arrestin-2-dependent signaling to chemotaxis is the likely pathway underlying this response [20]. This supposition is supported by several in vitro reports which demonstrate that chemotaxis of immune and other cell types is promoted by β -arrestin-dependent activation of MAPK signaling pathways [33].

β_2 -ARs functionally regulate lung structural cells in the context of allergic asthma [30,34]. Thus, it is plausible that in these cell types constitutive, or agonist-mediated, activation of a β_2 -AR- β -arrestin-dependent signaling pathway is required for the asthma phenotype to develop. In particular, airway epithelial MAPK signaling has been found to be important in expression of the asthma phenotype in mice [35] and MAPKs are prominently activated by β -arrestin-2 [36]. Additionally, airway epithelial cells express significantly more β_2 -AR and β -arrestin-2 [37] than airway smooth muscle cells. We cannot, however, rule out the possibility that airway smooth muscle cells may also, or alternatively, contribute to the development of the asthma phenotype through a β_2 -AR-mediated β -arrestin-dependent signaling pathway. For example, McGraw and Liggett showed in untreated mice that airway hyperresponsiveness results from persistent constitutive β_2 -AR-mediated up-regulation of PLC- β 1 expression [38]. It is plausible that the β -arrestin-dependent signaling pathway, known to regulate gene transcription [36], underlies this effect since airway hyperresponsiveness requires lung structural cell β -arrestin-2 expression.

Further delineation of the cell types that require β_2 -AR and β -arrestin-2 expression for asthma phenotype development will provide mechanistic information essential to the treatment of this disease. To this end, future research can utilize the finding that although both the β -arrestin-dependent and G protein-dependent signaling pathways generate similar downstream effectors distal to β_2 -AR activation, they can still be distinguished by examining the spatial and temporal aspects of the signaling cascade [39].

Clinical studies of the benefits and safety of treatment of asthma with β_2 -AR inverse agonists

Because β -blockers are currently contraindicated in asthma, they are underutilized in this population even in those patients with cardiac risk factors who may benefit from them [40•]. This results from the fact that their acute administration can produce bronchoconstriction and worsen asthma symptoms. However, several recent reports confirmed the safety and potential beneficial effects of cardioselective β -blockers when administered to treat cardiac comorbidities in patients with asthma or COPD [41–44]. However, the effects of chronic administration of β -adrenoceptor inverse agonists in the treatment of asthma has remained unknown until recently [45]. In a pilot study, we investigated the safety and efficacy of chronic administration of the non-selective inverse agonist, nadolol, in 10 patients with mild asthma. Dose escalation of nadolol was performed based on stringent cardiovascular and pulmonary function criteria [46••]. Chronic nadolol dosing was well tolerated and produced a dose-dependent increase in the PC20 of methacholine when administered over 9 weeks. A second study including ten more patients has now been completed supporting these results (Nicola Hanania, personal communication). These findings now need to be replicated in large placebo-controlled trials. Furthermore, the mechanism(s) of these beneficial effects in humans needs to be explored in these studies.

Conclusions

These results emphasize two important concepts. One is that duration of treatment with β -AR ligands plays a critical role in the clinical response in asthma and CHF. This temporal effect appears to be reciprocal between agonists and inverse agonists. β -AR agonists have acutely beneficial effects while inverse agonists have acutely detrimental effects. However, with chronic use the results reverse; agonists become detrimental, while inverse agonists become beneficial. The second concept is that it is likely that inhibition of signaling via the non-canonical β -arrestin-2 pathway is responsible for the results observed in the murine asthma models following chronic treatment with β_2 -AR inverse agonists. Thus, it is possible that in asthma, β_2 -AR agonists exert their beneficial effect on airway smooth muscle cells to achieve bronchodilation through canonical cAMP-mediated signaling, and β_2 -AR inverse agonists exert their beneficial effects on airway epithelial cells and immune cells by inhibiting constitutive pro-inflammatory signaling through non-canonical β -arrestin-2-mediated signaling.

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- of special interest

• of outstanding interest

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Intrinsic Activities of β_2 -Adrenoceptor Ligands

Figure 1.

The intrinsic activity of ligands at the β_2 -AR. Intrinsic activity is a system-dependent relative value where the agonist providing the largest response is assigned a value of 100% (in this case epinephrine). With the discovery of inverse agonists it has been extended into negative values. Here the inverse agonist values used are the percent inhibition of left atrial tension in a transgenic mouse with cardiac-specific overexpression of the β_2 -AR. In this model the overexpression resulted in a sufficient number of spontaneously active receptors to increase atrial contractility to a level comparable to that seen in a wild type mouse following a maximal concentration of epinephrine [17,27,47,48].

Alternative Signaling by β_2 AR

Figure 2.

Alternative signaling by β_2 -ARs. Activation of β_2 -AR leads to both β -arrestin-dependent and G protein-dependent signaling. Acute β_2 -AR activation attenuates the asthma phenotype via the G protein-dependent pathway in airway smooth muscle cells. The asthma inflammation phenotype is significantly diminished when β_2 -AR or β -arrestin-2 is absent or when a β_2 -AR inverse agonist is chronically administered. The dotted lines represent a proposed pathway underlying the asthma phenotype that requires activation of a β_2 -AR-mediated β -arrestin-2-dependent signaling pathway. (β_2 -AR, beta-2-adrenergic receptor; β arr2, β -arrestin-2; KO, knock-out; MAPK, mitogen-activated protein kinase; AHR, airway hyperresponsiveness; ASM, airway smooth muscle).