Agonizing over agonism: Should asthmatics turn their β-receptors on or off?

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Since the development of albuterol >4 decades ago (1), agonists selective for the β_2-adrenergic receptor (β_2AR) have been the drug of choice for relief of life-threatening bronchospasm experienced by asthmatics. Both short- and long-acting β_2AR agonists (SABAs and LABAs, respectively) have also been used extensively for the prophylactic management of asthma symptoms. The therapeutic efficacy of β_2AR agonists relates to their ability to directly relax airway smooth muscle to cause airways to dilate and conduct greater airflow. Yet increasing concerns that chronic use of β_2AR agonists actually increases mortality in asthmatics have culminated in a recent (and controversial) recommendation by an FDA advisory panel that the risks of two widely-prescribed LABAs outweigh their benefits. Why such risks may exist has puzzled both researchers and clinicians. Some have pointed to tolerance to β-agonists caused by desensitization of airway β_2ARs (2). Others have asserted that β-agonists have no direct toxic effects yet their ability to provide symptomatic relief masks an increasing level of airway inflammation (3). In this issue of PNAS, Nguyen *et al.* (4) shed new light onto the role of β_2AR agonism in asthma and suggest the paradoxical notion that blocking β_2ARs may be a more effective strategy for managing asthma (see Fig. 1).

An analogous paradigm shift in the management of congestive heart failure (CHF) was proposed in 1975 when Waagstein *et al.* (5) demonstrated that chronic administration of β-blockers to CHF patients improved their clinical condition and reversed maladaptive heart remodeling. It had been previously presumed that the pump function of the weak, failing heart could be treated by stimulation with synthetic β-agonists such as dobutamine. Since then we have learned that although β_1-Adrenergic receptor (β_1AR) agonism can acutely increase cardiac contractility, it is also central to the pathogenesis of heart failure. By blocking β_1ARs with β-blockers the heart is spared from the excessive work and various biochemical mechanisms that cause a large, hypodynamic heart (6).

Similar to studies demonstrating the role of β_1AR agonism in CHF, Nguyen

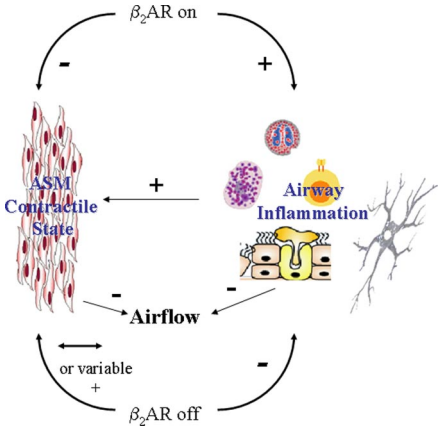

Fig. 1. β_2AR agonism in the asthmatic airway, a potential model suggested by findings of Nguyen *et al.* (4). β_2AR activation ("β_2AR on"), resulting from constitutive β_2AR activity, endogenous catecholamines, or inhaled β-agonists, has a permissive effect on airway inflammation that generates contractile agents causing airway smooth muscle (ASM) contraction and promotes airway mucus secretion that increases airway resistance. Direct effects of β-agonists on ASM antagonize effects of contractile agents to prevent/reverse bronchoconstriction. Airflow conductance is affected by the competitive actions of procontractile and prorelaxant effects on ASM, and by impedance caused by airway mucus. Alternatively, β_2AR inverse agonists ("β_2AR off") inhibit all β_2AR activity, resulting in inhibition of allergic inflammation and null or modest inhibition the bronchoprotective/relaxing effect of β_2AR activity in ASM. ASM contractile state and airflow are effectively managed by the anti-inflammatory effects that reduce levels of bronchoactive agents and mucus.

et al. (4) suggest that β_2AR agonism is pathogenic in asthma. Experiments used both genetic and pharmacological strategies to examine the effect of blocking β_2ARs on the development of antigen-induced, asthma-like properties in the mouse. After a period of sensitization and challenge with antigen, mice lacking the gene for the β_2AR developed significantly lesser airway hyperresponsiveness (AHR) and airway inflammation than did control mice. Chronic administration to control mice of nadolol, which has properties of a β_2AR "inverse" agonist, produced results qualitatively similar to those observed with β_2AR gene knockout. Inverse agonists are a class of antagonists that not only can block the ability of agonists to bind and activate a receptor but also can lock a receptor in a "closed" conformation and thereby block any (unliganded) constitutive or spontaneous activity of the receptor. This mechanism is in contrast to that of neutral antagonists, which can only block access of agonists to the receptor (7). Interestingly, chronic administration of the β_2AR antagonist alprenolol failed to affect either AHR or airway inflammation induced by antigen in control mice. These findings suggest that inverse agonism of the β_2AR is key to eliminating the permissive effect of β_2ARs on antigen-induced asthma properties.

These novel data identify the β_2AR as the key target mediating the effects of inverse β-agonists in this model, and extend previous studies by Bond and coworkers (8–10) suggesting a possible therapeutic role for β_2AR inverse agonists in asthma. Asthma is a complex disease in which an exaggerated immune response to inhaled antigen results in airway inflammation that causes the smooth muscle surrounding the airways to contract excessively. For most asthmatics this bronchospasm can be rapidly reversed by inhalation of SABAs such as albuterol. Some LABAs can also provide rapid relief, although LABAs are used primarily as maintenance prophylactic drugs to prevent the occurrence of bronchospasm. Although SABAs/LABAs are effective in managing this critical asthma symptom, their ability to address the primary cause of bronchospasm—airway inflammation—is unclear. Some studies have suggested that β_2AR agonists have anti-inflammatory properties with respect to inflammatory cell functions, whereas others have ascribed pro-inflammatory effects of β_2AR agonists on inflammatory cells or airway inflammation (reviewed in ref. 11). An underlying rationale for the use of combined inhaled LABA and corticosteroid therapy in asthma is that corticosteroids are highly effective in controlling airway inflammation.

Interestingly, the findings of Nguyen *et al.* (4) suggest that minimal β_2AR agonism is sufficient to enable significant antigen-induced airway inflamma-

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tion and AHR. Alprenolol, which lacks inverse agonist properties but can function as a β_2AR antagonist, was ineffective in attenuating either indices of airway inflammation or AHR. Although interpretation of these results is confounded by the potential of alprenolol to function as a partial agonist, it appears safe to conclude that β_2AR agonism caused by either constitutive activity of the β_2AR or a very low level of agonist-induced receptor activation permits the inflammatory effects of antigen in this model. Numerous basic science and clinical questions are prompted by this pro-inflammatory effect of β_2AR agonism and the use of β_2AR inverse agonists in asthmatics.

(*i*) Through which cells does β_2AR agonism promote airway inflammation? Induction of airway inflammation in asthma is a complex process involving the participation of numerous cell types. Some inflammatory cells, such as type 2 T cells, exhibit β_2AR-agonist-promoted pro-inflammatory properties when examined in vitro (11). However, such properties cannot be readily extrapolated to the in vivo condition, and experimental approaches for testing in vivo relevance, especially in humans, are technically challenging.

(*ii*) What signals, leading to what cell functions, do β_2ARs transduce to promote airway inflammation? Classical β_2AR signaling involves events leading to the activation of the cAMP-dependent protein kinase. However, there is a growing appreciation that β_2ARs signal through alternative pathways, including those dependent on other cAMP effectors, G_i G proteins, or arrestins (7). Should specific β_2AR signaling events be associated with pro-inflammatory effects of β-agonists, the possibility exists of targeting these downstream events for inhibition, or alternatively using specific β_2AR ligands that induce qualitatively different signaling (12).

(*iii*) Can β_2AR inverse agonists be safely administered to asthmatics? As was the case when β-blockers were originally proposed for the treatment of CHF, major concerns exist regarding the safety of β_2AR inverse agonists as a treatment for asthma. β-Blockers are generally contraindicated in asthma because of early studies demonstrating that β-blockers caused bronchospasm in asthmatics (13). Similarly, β-blockers had been contraindicated in CHF because short-term treatment with β-blockers resulted in a worsening of CHF symptoms. Whether treatment of asthmatics with β_2AR inverse agonists results in a brief period of adverse effects followed by improved asthma control remains to be determined. A recent pilot study examining nadolol effects in 10 mild asthmatics reported 4 subjects as experiencing a moderate drop in expired airflow after their first dose of nadolol (9). However, after 9 weeks of treatment, mean values for expired airflow were greater than those measured at baseline, and a significant reduction in the sensitivity to the bronchoconstricting agent methacholine was observed.

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Additional safety questions involve the asthmatic population(s) suited for treatment with β_2AR inverse agonists, and which rescue medications are most appropriate for asthmatics on β_2AR inverse agonists. β_1AR–selective β-blockers are relatively safe in patients with mild asthma (14), and based on the pilot study results described above safety concerns may be limited in mild asthmatics taking β_2AR inverse agonists. However, severe asthmatics appear more susceptible to bronchospasm induced by β-blockers (13). Given the increased likelihood of an adverse event during initial treatment with β_2AR inverse agonists, rescue medications will assume greater importance. Anticholinergics are one rescue medication option because their efficacy in reversing bronchospasm induced by β-blockers has been demonstrated (15). Another interesting possibility is high-affinity β_2AR agonists, which could effectively compete with β_2AR inverse agonists for occupancy of β_2ARs on airway smooth muscle to promote bronchorelaxation. Moreover, the signaling capacity of agonist-activated β_2ARs is predicted to be increased as a result of chronic treatment with β_2AR inverse agonists, which causes an up-regulation of β_2AR density in the lung (16).

Ultimately, numerous clinical issues will need to be resolved in human studies to establish β_2AR inverse agonists as viable asthma drugs. Equally challenging are the basic science questions regarding the complexity of β_2AR signaling and function in the lung.

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