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Clinical Implications of the Intrinsic Efficacy of Beta-Adrenoceptor Drugs in Asthma: Full, Partial and Inverse Agonism

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Abstract

Purpose of the Review— β_2 -adrenoceptor (AR) agonists are the most effective bronchodilators known, and play important roles in every step of asthma therapy. The intrinsic efficacy is an important pharmacological property that differentiates the clinical effects and safety profile of β_2 AR agonists. We review the role of β_2 -AR agonist intrinsic efficacy in asthma treatment focusing on recent literature.

Recent Findings—In acute asthma, a *full* agonist (high intrinsic efficacy) offers a clinical advantage over a *partial* agonist (low intrinsic efficacy) but with the potential of inducing dose-dependent adverse effects. The chronic use of β_2 -AR agonists may be associated with several adverse outcomes including loss of asthma control and even increased mortality. Recently, the role of β AR *inverse* agonists (beta-blockers) which have a negative intrinsic efficacy was studied. While contraindicated in acute asthma, preliminary data suggest that the chronic use of these agents may be associated with attenuation of airway hyperresponsiveness in patients with mild asthma. Studies in a murine model of asthma suggest that such effects may be related to decreased airway inflammation and mucous metaplasia.

Summary—Rational choice among β_2 AR agonists in acute and chronic asthma should be influenced by differences in intrinsic efficacy among these agents. In acute severe asthma, a *full* agonist offers a clinical advantage over a *partial* agonist. While the use of *inverse* agonists in the treatment of asthma is still experimental and needs further exploration in future trials, preliminary studies suggest that their chronic use is safe and is associated with decreased airway hyperresponsiveness.

Keywords

asthma; β -blocker; β -adrenoceptor inverse agonist; β_2 -adrenoceptor agonist; chronic

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Introduction

Asthma is a chronic inflammatory disorder of the airways characterized by airway hyperresponsiveness (AHR) and airflow obstruction. The National Asthma Education and Prevention Program (NAEPP) guidelines established a number of asthma management goals that focus on achieving and maintaining asthma control (1). Asthma control is achieved by minimizing impairment and reducing risk of exacerbations, lung function decline and adverse effects (1). To achieve these goals, a six-step pharmacological algorithm for treatment of asthma has been recommended. β_2 AR agonists are the most powerful known bronchodilators and play a pivotal role in every step of this algorithm. While these agents were first used thousands of years ago, progress in drug development has resulted in safer, longer-acting and β_2 AR-specific agents(2). β_2 AR agonists act by binding to the β_2 AR, which is a member of the seven transmembrane domain, G protein-coupled family of receptors (GPCRs). Although β_2 ARs are present in high density in airway smooth muscle cells, they are also present in a multitude of other tissues and cell types including submucosal glands, airway epithelial cells, vascular endothelium, mast cells, circulating inflammatory cells such as eosinophils and lymphocytes, type II pneumocytes and cholinergic ganglia. Therefore, these agents may have other potential non-bronchodilator effects such as anti-inflammatory properties (3), although the clinical implications of such effects are still debatable(4). Numerous β_2 AR agonists of differing pharmacologic properties are available for clinical use and several more are currently in development for use either as stand-alone drugs (5) or in combination with inhaled corticosteroids (6). Clinicians typically base their choice of a particular agent on parameters of receptor selectivity, onset and duration of action, but rarely consider another very important pharmacologic characteristic - the intrinsic efficacy.

Pharmacologic Differences Among β AR Agonists

β_2 AR agonists are classified by their onset and duration of action, receptor selectivity, affinity, potency and efficacy(2). The *onset of action* of inhaled β_2 AR agonists is primarily influenced by their lipophilicity (the higher the lipophilicity the slower onset of action) and kinetics of binding. Among the agents currently in use, albuterol and formoterol have a more rapid onset of action than salmeterol. *Duration of action* is similarly influenced by lipophilicity and binding kinetics, as well as by resistance to clearance. Both salmeterol and formoterol have a longer duration of action than albuterol as their lipophilicity produces a depot effect at the cell membrane allowing for their twice daily administration. *Receptor selectivity* is also an important pharmacologic characteristic, however all currently used β_2 AR agonists are moderately to highly selective β_2 AR. *Affinity* refers to the attraction between the agonist and its receptor and is most commonly expressed as the dissociation constant between agonist and receptor. *Potency* refers to the concentration of a drug that achieves the half maximal response of which that drug is capable (EC_{50}), and is dependent upon the affinity and intrinsic efficacy of the drug.

Intrinsic Efficacy refers to the ability of a drug to activate its receptor, without regard for drug concentration or receptor numbers as it is defined as efficacy/total receptor number (2). Receptor activation may be measured as a conformational change by physical techniques, as a biochemical response to activation of the signal transduction pathway downstream of the receptor, or as a physiologic response. Measured efficacy depends on variable factors in the target cell, such as receptor number or the presence of functional antagonism (i.e., activation of an opposing signal transduction pathway). In a cell with high receptor numbers, activation of only a small fraction of receptors suffices to generate a full response. Conversely, in a cell with low receptor number or in the presence of functional antagonism, activation of even a high fraction of receptors may not yield a full relaxation response.

To better understand the differences between *full*, *partial* and *inverse* agonists, it is useful to consider the two-state receptor model. G-protein-coupled receptors are thought to exist in an equilibrium between an inactive conformation (R), and a spontaneously active conformation (R*), Classic agonists have a high affinity for R* relative to their affinity for R and increase the concentration of R*. In this model intrinsic efficacy is defined as the relative affinity preference of ligands for R and R* (Figure 1). Highly efficacious drugs (*full agonists*) have much higher affinity for R* than R, while agonists with low intrinsic efficacy (*partial agonists*) have a relatively small affinity preference for R* relative to R. Among currently available β_2 AR agonists, epinephrine has the highest intrinsic efficacy followed by formoterol then by albuterol and finally salmeterol which has the lowest intrinsic efficacy. It is of interest that almost all novel β_2 AR agonists under development have a high intrinsic efficacy comparable with that of formoterol (5). In this model, *inverse* agonists (negative intrinsic efficacy) have a high affinity for the R conformation relative to the R* and decrease the concentration of the R*, exerting the exact opposite effects of agonists. Finally, neutral competitive antagonists have equal affinity for R and R* and do not displace the equilibrium but competitively antagonize the effects of both agonists and inverse agonists (Figure 1)(7).

Clinical Implications of *Full* vs. *Partial* β_2 AR Agonists in Asthma

Because β_2 AR agonists can act rapidly and are the most effective bronchodilators available, their use is a cornerstone of the initial management of acute asthma exacerbations. The severity of acute asthma ranges from mild exacerbations that readily respond to initial therapy in the emergency department, to severe, life-threatening exacerbations requiring intubation and admission to the intensive care unit (8). Therefore, a single agent, a standard dose, and a particular route of delivery are not appropriate for all settings. In the majority of cases, an inhaled rescue drug such as albuterol, given more frequently and in higher doses than for simple rescue, will suffice. However, in a patient with impending respiratory failure despite the administration of high doses of a rescue medication when β_2 AR are desensitized by prior use of β_2 -agonists and functionally antagonized by inflammatory mediators that are present during an acute exacerbation, a *full* agonist has advantages over a *partial* agonist (Figure 2) (9-11). In the chronic setting, agonists of high intrinsic efficacy such as formoterol have dose-dependent effects on bronchoprotection an effect that is not seen with salmeterol (12).

Safety of β_2 AR Agonists in Asthma

Adverse effects of β_2 AR agonists are largely due to activation of β_2 AR in non-target tissues. Cardiac stimulation leads to tachycardia and arrhythmias, while skeletal muscle stimulation leads to tremor and hypokalemia. Non-target tissues, such as skeletal muscle and the heart, have a lower β_2 AR density than airway smooth muscle. This accounts, in part, for the excellent side-effect profile of partial agonists such as albuterol, because there are sufficient spare receptors in the target tissue for full cell activation by a partial agonist but not in non-target tissues(2). Furthermore, the desensitization that occurs during the first few days of regular use of a β_2 AR agonist results in further reduction in the responsiveness of non-target tissues, accounting for the commonly observed resolution of side effects, such as tachycardia and tremor, after the first few doses. In view of the low receptor density of non-target tissues, it might be expected that full β_2 AR agonists would elicit a response greater than partial agonists in non-target tissues, and this is indeed the case. In dose-response studies, full agonists with high intrinsic efficacy have been demonstrated to be capable of causing more adverse effects, such as greater tachycardia and reduction in serum potassium, than partial agonists(12-14). Tolerance to the bronchoprotective properties of β_2 AR agonists and modest but non-progressive tolerance to their bronchodilator effects have been seen. The regular use of short-acting β_2 AR agonists has been associated with increased airway hyperresponsiveness, loss of asthma control and even increased asthma mortality (15). Recent data show similar associations

with regular use of long-acting β_2 AR. It is of interest that the most dramatic spikes in asthma mortality were observed with the use of high-dose formulations of β_2 AR agonists of high intrinsic efficacy, isoproterenol and fenoterol (15). These adverse effects may be more pronounced in certain individuals with homozygous arginine genotype at position 16 of the β_2 AR (one sixth of Caucasians and one fifth of African Americans in the U.S.)(16;17).

More recently, the safety of regular use of long-acting β_2 AR agonists (both low and high intrinsic efficacy agents) has also been questioned (18-21). This issue was amplified by the results of a study (SMART) which suggested an association between the regular use of salmeterol with an increase asthma-related deaths and life-threatening experience (22). Other studies questioned the safety of formoterol in asthma (23) and a recent metanalysis did not have enough power to rule out any signal of increased mortality with formoterol (24). On the other hand, several observational studies failed to confirm these findings in patients treated with long acting β_2 AR agonists who are taking inhaled corticosteroids (25-27) (28;29).

The exact mechanisms for this safety issue with chronic use of β_2 AR agonists in asthma remain unknown. Potential mechanisms include the increase in airway inflammation (30), airway hyperresponsiveness (31;32), competitive antagonism of the β_2 AR causing subsensitivity to albuterol (33) and the increase in brain-derived neurotrophic factor (BDNF) (32). Furthermore, although some studies suggested that adverse effects occur more frequently in some patients with homozygous arginine 16 genotype (34) (35) (36), other studies failed to confirm this observation with the use of long-acting β_2 AR agonists (37;38).

Inverse β AR Agonists (β -blockers) in Asthma

Inverse agonists exert opposite effects to agonists. However, the clinical effects of agonists and inverse agonists are highly dependent on the duration of therapy (39)(Figure 3). This paradox was first described in congestive heart failure (CHF) where the acute administration of a β_2 AR agonist is beneficial; however its chronic administration is deleterious to cardiac function and increases mortality. The opposite occurs with the use of an inverse agonist (β -blocker) which has an acute deleterious effect but chronically beneficial effect on survival (40). The same analogy is observed with β_2 AR agonists in asthma where their acute administration is beneficial to lung function and symptoms, but their chronic use is associated loss of asthma control and increased mortality. *Inverse* agonists are currently contraindicated in asthma and thus are underutilized in this population, even in those patients with cardiac risk factors who may benefit from them (41). This results from the fact that the acute administration of these drugs can produce bronchoconstriction and worsening of asthma symptoms (42). However, several recent reports demonstrated the safety and potential beneficial effects of cardioselective beta-blockers when administered to treat cardiac comorbidities in patients with asthma or COPD (43-46). The effects of chronic administration of inverse β -agonists in the treatment of asthma has remained unknown until recently. Recent studies using a murine model of asthma showed that while acute (single dose) administration of β AR inverse agonists increased airway hyperresponsiveness (AHR), their chronic (28 day) administration had an opposite effect and decreased AHR (47). Furthermore, chronic treatment with β AR inverse agonists produces broad anti-inflammatory effects, and especially dramatic effects on airway epithelium and mucous metaplasia (48;49). These results have been confirmed using β_2 AR null mice demonstrate a pivotal role of the β_2 AR for full development of mucous metaplasia and other features of asthma (50). In human asthma, the effect of chronic administration of the inverse β AR agonist, nadolol, on airway hyperresponsiveness in 10 patients with mild asthma was recently reported (51). Nadolol produced a dose-dependent increase in the PC₂₀ methacholine. The significance of these above findings in animal models and humans subjects, if confirmed in additional studies, may provide a paradigm shift in the chronic management of asthma (52-54).

Conclusion

Intrinsic efficacy is a key pharmacologic parameter that differs dramatically among available β -agonists. β_2 AR agonists of high Intrinsic efficacy offer advantages over weak agonists in emergency management of asthma though their use is associated with dose-dependent adverse effects. The long-term use of both short- and long-acting β_2 AR agonists, especially when used without concomitant steroids, can be associated with worsening asthma control, increased airway hyperresponsiveness and increased mortality. β AR inverse agonists may have beneficial effects in the chronic treatment of asthma but this needs further evaluation.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

* Of special interest

** Of outstanding interest

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Figure 1. Schematic representation of the effects of a full agonist, a partial agonist and an inverse agonist

Some receptors have measurable constitutive activity even in the absence of an agonist. The addition of an agonist to the system shifts the receptor conformation to the active conformation (R^*). This is more pronounced with a full agonist than with a partial agonist. When an antagonist is added (in the absence of an agonist), it produces no effect (intrinsic efficacy = 0). However if an inverse agonist is added, it inhibits the constitutive (basal) activity of the receptor (negative intrinsic efficacy) and shifts the receptor away from the active conformation (R^*) to the inactive conformation (R).

Figure 2.
Schematic Representation for the Potential Differential Effects Between Full and Partial Beta-Agonists on Airway Smooth Muscles During Remission and During an Acute Severe Exacerbation of Asthma (modified from (9))

Figure 3. Effect of Duration of Exposure for an Agonist or an Inverse Agonist on Clinical Effects β -agonists can be acutely beneficial but chronically can induce desensitization of the receptor, while inverse agonists (beta-blockers) are acutely detrimental but chronically beneficial (adapted from (39)).