



BETA-ADRENERGIC AGONIST AS PRINCIPAL BRONCHODILATOR AGENT: A REVIEW

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ABSTRACT

Beta-agonists, the cognate ligand of the β_2 adrenoceptor, have been used as bronchodilators for over thousands of years, and they remain today the frontline treatment for asthma and Chronic Obstructive Pulmonary Disease (COPD). The β -agonists used clinically today are the products of significant expenditure and over a hundred year's intensive research aimed at minimizing side effects and enhancing therapeutic usefulness. Inhaled β_2 -adrenoceptor (β_2 -AR) agonists are considered essential bronchodilator drugs in the treatment of bronchial asthma, both as symptoms-relievers and, in combination with inhaled corticosteroids, as disease-controllers. β adrenergic receptors are coupled to a stimulatory G protein of adenylyl cyclase. This enzyme produces the second messenger cyclic adenosine monophosphate (cAMP). In the lung, AMP decreases calcium concentrations within cells and activates protein kinase A. Both of these changes inactivate myosin light chain kinase and activate myosin light-chain phosphatase. Beta-adrenoceptor agonists (beta -agonists) are among the most used substances in competitive sports. World Anti-Doping Agency restricts the use of all selective and non-selective beta -agonists in and out of competition with few exemptions. Formoterol, salbutamol, and salmeterol are allowed by inhalation within defined dosing limits. These restrictions are in place because supratherapeutic use of beta - agonist has the potential to be anabolic and to enhance performance, as well as due to potential side effects. In the present review the potential role of beta agonist have been analyzed with respect to its bronchodilator role in the treatment of asthmatic conditions.

KEYWORDS: Beta-agonist, Muscle, G protein, Asthma, Bronchodilator.

INTRODUCTION

The early 1900s marked the advent of epinephrine as a form of treatment in Western medicine after successfully obtaining it from the adrenal gland; this became the treatment for asthmatic patients until its replacement in the 1940s with the formulation of isoproterenol, a non-selective beta-adrenoreceptor agonist. However, the adverse side effects of isoproterenol became an issue of concern, and the search continued for treatment with a better side effect profile. With the discovery of the α_1 , α_2 , β_1 , β_2 receptors in subsequent years, it became known that airway bronchodilation had a strong correlation specifically with β_2 receptors in the lung vasculature. Pharmacological pursuits turned towards maximizing the selectivity towards the β_2 receptor in an attempt to reduce the incidence of adverse side effects of the non-selective isoproterenol. These new drugs, classified as β_2 adrenergic receptor agonists, have since become frontline treatments for bronchial asthma and chronic obstructive pulmonary disease (COPD). Subsequent research continues to aim at

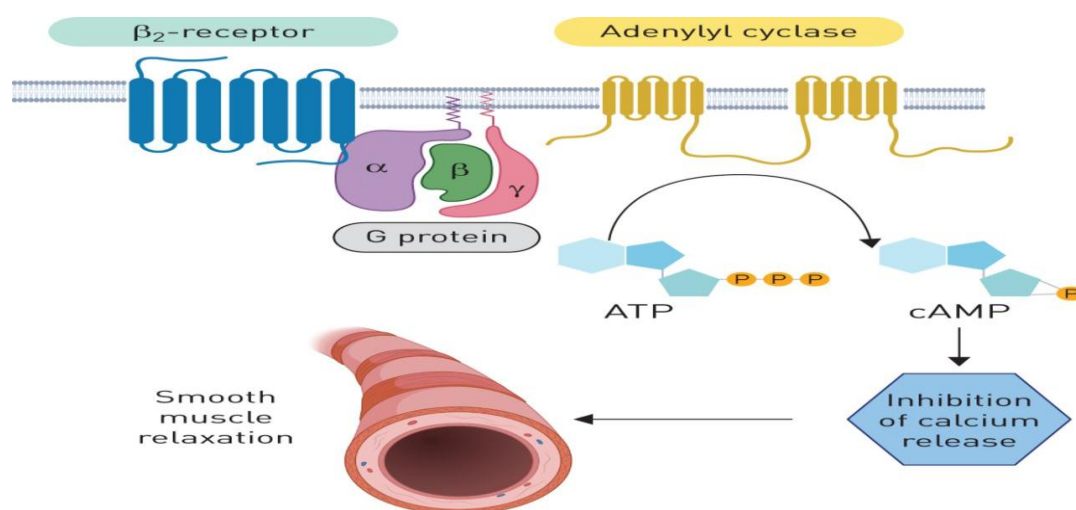
improving the efficacy, minimizing adverse effects, with the goal to decrease symptoms, mortality rates, and improve patient quality of life (Billington et al 2013). However, since the discovery of β_2 agonists, there have been many discussions regarding the potential long-term risks versus benefits to the overall rate of morbidity and mortality. β_2 -Adrenergic receptor agonists (β_2 -agonists) are widely used clinically to relax airway smooth muscle and are the principal bronchodilator agents used to treat bronchial asthma. Regular administration of short-acting β_2 -agonists may cause not only a deterioration of asthma control and an exacerbation of airway hyperreactivity, but also an accelerative decline in lung function in patients with this disease (Sear et al 1990). These undesirable dysfunctions may be due to reduced responsiveness to short-acting β_2 -agonists elicited by excessive exposure to these agents, a phenomenon referred to as desensitization (Barnes 1995). Moreover, a decline in β_2 -agonist activity is observed after prolonged exposure to pro-inflammatory cytokines and lysophospholipid (Kume et al 2001) that

participate in the airway inflammation of bronchial asthma. A postmortem study also has shown that the response to β_2 -agonists *in vitro* is attenuated in airway smooth muscle harvested from patients with fatal asthma. The impaired β_2 -adrenergic action is a characteristic feature of patients with this disease, and is an important problem in both the pathogenesis and therapy (Bai1990).

Mechanism of action

Circulating catecholamines activate adrenergic receptors as part of our functional autonomic system to produce parasympathetic and sympathetic physiological responses. Mimicking catecholamines, beta-2 agonists act as ligands to adrenergic receptors with increased selectivity towards beta-2 adrenergic receptors. The activation of the beta-2 adrenergic receptor initiates a transmembrane signal cascade, which involves the heterotrimeric G protein, Gs, and the effector, adenylyl cyclase (Fig.1). Adenylyl cyclase then increases intracellular cAMP via the hydrolysis of ATP. The

elevated cAMP concentration serves to activate cAMP-dependent protein kinase A (PKA). PKA can phosphorylate intracellular substrates, which modulate various effects within the cell. Specifically, in airway smooth muscle, PKA acts to phosphorylate Gq-coupled receptors leading to a cascade of intracellular signals which have been proposed to reduce intracellular Ca_2^+ or decrease the sensitivity of Ca_2^+ (Billington et al 2013). The change in Ca_2^+ results in the inhibition of myosin light chain phosphorylation, subsequently preventing airway smooth muscle contraction. This action is the underlying mechanism behind beta-2 agonists, which promotes the bronchodilatory effects used to treat many common respiratory diseases. There have been proposals that beta-2 agonists also provide anti-inflammatory effects within the airway smooth muscle through the reduction of intercellular adhesion molecule-1, the reduction of granulocyte-macrophage colony-stimulating factors release, stabilization of mast cell degranulation, and through the inhibition of multiple inflammatory pathways (Barisione et al 2010).



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Figure 1: Diagram showing the mechanism of action of the β_2 -receptor. The G protein-coupled receptor is activated by agonist binding, leading to conversion of ATP to cAMP by adenylyl cyclase, and downstream inhibition of intracellular calcium release, and subsequent bronchial smooth muscle relaxation.

Classification

Onset of action and duration determines the classification of beta-2 agonists. The classes separate into short-acting beta-agonists (SABAs), long-acting beta-agonists (LABAs), and, most recently, ultra-long-acting beta-agonists (ultra-LABAs). As the names suggest, SABAs have the shortest half-life and are for immediate symptomatic relief. LABAs, along with ultra-LABAs, provide prolonged, sustained treatment due to their increased half-life. The different properties between these classes occur through modifications of the molecular structure of the drugs. For example, the prolonged duration is achievable by decreasing the susceptibility of the beta-2 agonists to catechol O-methyltransferase (COMT) and monooxidase enzymes that induce oxidative deamination and methylation, thereby inactivating the beta-2 agonist.

Short-acting Beta-agonists(SABAs)

SABAs are the first-line medications for acute treatment in asthma symptoms and exacerbations. They are also commonly used in conjunction with LABAs, inhaled corticosteroids, or long-acting muscarinic agonists in treatment for COPD. Typical administration of these agents is inhalation via metered dosing or dry powder inhalation. Compared to the alternative oral administration, inhalation has an increase in therapeutic value, as well as a decrease in systemic side effects (Barisione et al 2010). The hallmark SABA is the drug salbutamol, which has an onset of action of under 5 minutes, and a therapeutic effect duration between 3 to 6 hours. While most commonly used as airway treatment, nebulized albuterol is also useful as a treatment for hyperkalemia by providing a rapid shift of intracellular potassium (Effa et al 2017). Terbutaline is a commonly

used short-acting beta-2 agonist as a tocolytic in the cessation of labor contractions. Common SABAs are Salbutamol (albuterol), Terbutaline, Levalbuterol and Pirbuterol.

Long-acting Beta-agonists (LABAs)

LABAs are used in treatment for patients with asthma and COPD as well, often in conjunction with inhaled corticosteroids given there is evidence of greater efficacy with dual therapy versus monotherapy LABA (Rodrigo et al 2017). They have an onset of duration greater than 5 minutes compared to the SABAs, with up to 15 minutes for salmeterol, and duration of effect for at least 12 hours. Similar to SABAs, the recommended route of administration for LABAs is through inhalation. LABAs are generally added on as second-line treatment in asthma that has failed symptomatic relief with SABAs. Common LABAs are Salmeterol, Formoterol.

Ultra-LABAs

Ultra-LABAs have the greatest duration of effect, up to 24 hours, and they have the additional benefit of being a once-a-day treatment dosage. Indacaterol has been FDA approved as maintenance treatments for patients with COPD in combination with other bronchodilators. Indacaterol administration is as a dry powder with an onset of action around 5 minutes. Many other ultra-LABAs are currently undergoing research as well, with the potential to provide improvement to compliance and convenience compared to the current options of asthma and COPD treatments (Cazzola et al 2011). Common Ultra-LABAs are Indacaterol, odatrol, Vilanterol, Formoterol.

Administration

The major routes of administration for beta-2 agonists include metered dosed-inhalers, nebulizers, dry powder inhalers, orally, subcutaneously, or intravenously. The preferred route of administration for beta-2 agonists in the treatment of asthma and COPD is through inhalation. Inhalation localizes the drug to the lung tissue, concentrating the therapeutic effect on the airway smooth muscles while minimizing the distribution of the drug to the systemic circulation. There has been no correlation between the therapeutic effect of inhaled beta-2 agonists and the peak plasma levels of the beta-2 agonist (Matera et al 2018).

Issues of concern

Adverse effects of beta-2 agonists most commonly involve the desensitization of the beta-2 adrenergic receptor to the beta-2 agonist. Due to the similar properties between the classes of adrenergic receptors, beta-2 agonists can create an “off-target” effect in stimulating either alpha-1, alpha-2, or beta-1 receptors (Sear 2002). The most common side effects of beta-2 agonists involve the cardiac, metabolic, or musculoskeletal system. Due to the vasodilatory effect of peripheral vasculature and subsequent decrease in cardiac venous return, compensatory mechanisms

manifest as tachycardia are relatively common, especially within the first weeks of usage. Cardiac toxicity in the form of arrhythmias, cardiomyopathy, and ischemia have been correlated more strongly with older generation beta-2 agonists according to multiple reports ranging from single case reports to case-control studies (Salpeter et al 2004). Arrhythmias are seen more commonly in fenoterol usage versus albuterol, and arrhythmias have an increase in frequency in patients with underlying heart disease or concomitant theophylline use (Poukkula et al 1989). Beta-2 agonists have been shown to decrease serum potassium levels via an inward shift of potassium into the cells due to an effect on the membrane-bound Na/K-ATPase, which can potentially result in hypokalemia. Beta-2 agonists also promote glycogenolysis, which can lead to inadvertent elevations in serum glucose. Musculoskeletal tremors are a potential side-effect as well, found more commonly with the use of oral beta-2 agonists. The degree of which these adverse effects precipitate is generally associated with factors such as the selectivity ability of each beta-2 agonist to its respective receptor and the medication dosages. Several studies have also indicated hypoxemia and hypercapnia as exacerbating factors to the cardiotoxic effects of beta-2 agonists (Sear 2002). Multiple studies have reproduced a reduction in anti-bronchoconstriction from the extended use of salbutamol after the clinical induction of airway constriction with a methacholine test (Haney and Hancox 2005). However, clinical implications of tolerance in affecting the management of treatment are still under investigation. Theoretically, LABAs should result in increased tolerance compared to SABAs due to the continuous beta-receptor stimulation produced from their prolonged duration of action. However, this remains a topic of speculation, as studies have shown varying degrees of tolerance between both SABAs and LABAs (Twentyman 1992). Research has also suggested multiple external factors as influences of the degree of beta-2 agonist tolerance, including genetic polymorphisms of the beta-2 receptor, the degree of airway inflammation, and the route of medication delivery (Israel et al 2000).

Metabolic effects

Numerous studies have shown that the serum potassium level decreases with the use of inhaled or intravenous β -agonists. This reduction represents an intracellular shift of potassium rather than loss from the body. The shift in potassium is considered to be caused by stimulation of β ARs linked to the membrane-bound Na,KATPase on skeletal muscle, which causes an influx of potassium into the cells. Decreased serum potassium is aggravated by the use of corticosteroids and diuretics (Lipworth et al 1989), and the cardiac implications of hypokalemia may be aggravated by hypoxia. Hence, in situations of life-threatening asthma, there may be an increased risk of cardiac abnormalities associated with hypokalemia in the presence of corticosteroids and hypoxia. The decrease in serum potassium is dose-related and potency-related, with fenoterol having a more profound hypokalemic

effect than albuterol or formoterol (Bremner et al 1993) or terbutaline. In the latter study, mean decreases in serum potassium (SD) with high doses of fenoterol, albuterol, and Terbutaline. As with other pharmacologically predictable effects, tolerance has been demonstrated with repeated use (Lipworth et al 1900). Beta-Agonists increase glycogenolysis and hence increase plasma glucose. This is of minor importance, except in diabetic patients, whose disease is likely to be aggravated by the use of systemic corticosteroids in situations of severe asthma. The effect on glucose also shows tolerance with repeated use (Lipworth et al 1989).

CONCLUSION

Asthma and COPD are currently amongst the most prevalent respiratory diseases in the population.

Treatment and management begin with understanding the symptoms, confirmatory diagnostic tests, and proper assessment of the severity of the conditions. Beta-2 agonists are an integral part of the frontline management for symptomatic control, prevention of exacerbations, improving quality of life. Despite the debate over the use of beta2-adrenoceptor agonists in the treatment of airway disorders, the interest of pharmaceutical companies in the field is still high. However, it is difficult to determine whether this is due to the success that this class of bronchodilators still has, or just the fact that we are not yet able to identify a new class of bronchodilators that can control the bronchial muscle tone without being burdened by the risks of beta2-adrenoceptor agonists.

REFERENCES

- Bai TR. Abnormalities in airway smooth muscle in fatal asthma. *Am. Rev. Respir. Dis.* 1990; 141: 552-557.
- Barisione G, Baroffio M, Crimi E, Brusasco V, Beta-Adrenergic Agonists. *Pharmaceuticals*, 2010; 3(4): 1016-1044.
- Barnes PJ. Beta-adrenergic receptors and their regulation. *Am. J. Respir. Crit. Care Med*, 1995; 152: 838-860.
- Billington CK, Ojo OO, Penn RB, Ito S, cAMP regulation of airway smooth muscle function. *Pulm Pharmacol Ther*, 2013; 26(1): 112-120.
- Bremner P, Woodman K, Burgess C, et al. A comparison of the cardiovascular and metabolic effects of formoterol, salbutamol and fenoterol. *Eur Respir J*, 1993; 6: 204-210.
- Cazzola M, Calzetta L, Matera MG, $\beta(2)$ -adrenoceptor agonists: current and future direction. *Br J Pharmacol*, 2011; 163(1): 4-17.
- Effa E, Webster A, Pharmacological interventions for the management of acute hyperkalaemia in adults. *Nephrology*, 2017; 22(1): 5-6.
- Haney S, Hancox RJ, Rapid onset of tolerance to beta-agonist bronchodilation. *Respir Med*, 2005; 99(5): 566-71.
- Israel E, Drazen JM, Liggett SB, Boushey HA, Cherniack RM, Chinchilli VM, Cooper DM, Fahy JV, Fish JE, Ford JG, Kraft M, Kunselman S, Lazarus SC, Lemanske RF, Martin RJ, McLean DE, Peters SP, Silverman EK, Sorkness CA, Szeffler SJ, Weiss ST, Yandava CN, The effect of polymorphisms of the beta (2)-adrenergic receptor on the response to regular use of albuterol in asthma. *Am J Respir Crit Care Med*, 2000; 162(1): 75-80.
- Kume H, Ito S, Ito Y, Yamaki K. Role of lysophosphatidyl-choline in the desensitization of β -adrenergic receptors by Ca^{2+} sensitization in tracheal smooth muscle. *Am J Respir Cell Mol Biol*, 2001; 25: 291-298.
- Lipworth BJ, Clark RA, Dhillon DP, et al. Comparison of the effects of prolonged treatment with low and high doses of inhaled terbutaline on beta-adrenoceptor responsiveness in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis*, 1990; 142: 338-42.
- Lipworth BJ, McDevitt DG, Struthers AD. Prior treatment with diuretic augments the hypokalemic and electrocardiographic effects of inhaled albuterol. *Am J Med*, 1989; 86: 653-257.
- Lipworth BJ, Struthers AD, McDevitt DG. Tachyphylaxis to systemic but not to airway responses during prolonged therapy with high dose inhaled salbutamol in asthmatics. *Am Rev Respir Dis*, 1989; 140: 586-92.
- Matera MG, Rinaldi B, Page C, Rogliani P, Cazzola M, Pharmacokinetic considerations concerning the use of bronchodilators in the treatment of chronic obstructive pulmonary disease. *Expert Opin Drug Metab Toxicol*, 2018; 14(10): 1101-1111.
- Poukkula A, Korhonen UR, Huikuri H, Linnaluoto M, Theophylline and salbutamol in combination in patients with obstructive pulmonary disease and concurrent heart disease: effect on cardiac arrhythmias. *J Intern Med*, 1989; 226(4): 229-34.
- Rodrigo GJ, Price D, Anzueto A, Singh D, Altman P, Bader G, Patalano F, Fogel R, Kostikas K, LABA/LAMA combinations versus LAMA monotherapy or LABA/ICS in COPD: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis*, 2017; 17(12): 907-922.
- Salpeter SR, Ormiston TM, Salpeter EE, Cardiovascular effects of beta-agonists in patients with asthma and COPD: a meta-analysis. *Chest*, 2004; 125(6): 2309-21.
- Sears M, Taylor DR, Print CG et al. Regular inhaled beta-agonist treatment in bronchial asthma. *Lancet*, 1990; 336: 1391-1396.
- Sears MR, Adverse effects of beta-agonists. *The Journal of allergy and clinical immunology. J Allergy Clin Immunol*, 2002; 110(6): S322-8.
- Twentyman OP, Higenbottam TW, Controversies in respiratory medicine: regular inhaled beta-agonists - clear clinical benefit or a hazard to health? (1). Beta-agonists can be used safely and beneficially in asthma. *Respir Med*, 1992; 86(6): 471-6.