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Research and development of bronchodilators for asthma and COPD with a focus on G protein/K_{Ca} channel linkage and β_2-adrenergic intrinsic efficacy

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ABSTRACT

Bronchodilators are used to improve symptoms and lung function in asthma and COPD. Airway smooth muscle tone is regulated by both muscarinic and β_2-adrenergic receptor activity. Large-conductance Ca^{2+}-activated K^+ (K_{Ca}) channels are activated by β_2-adrenergic receptor agonists, via G_s, and suppressed by muscarinic receptor antagonists via G_i. This functional antagonism converges on the G protein/K_{Ca} channel linkages. Membrane potential regulated by K_{Ca} channels contributes to airway smooth muscle tension via Ca^{2+} influx passing through voltage-dependent Ca^{2+} (VDC) channels. The G_s/K_{Ca}/VDC channel linkage is a key process in not only physiological effects, but also in dysfunction of β_2-adrenergic receptors and airway remodeling. Moreover, this pathway is involved in the synergistic effects between β_2-adrenergic receptor agonists and muscarinic receptor antagonists. Intrinsic efficacy is also an important characteristic for both maintenance and loss of β_2-adrenergic action. Allosteric modulators of G protein-coupled receptors contribute not only to this synergistic effect between β_2-adrenergic and muscarinic M_2 receptors, but also to intrinsic efficacy. The effects of weak partial agonists are suppressed by lowering receptor number, disordering receptor function, and enhancing functional antagonism; in contrast, those of full or strong partial agonists are not suppressed. Excessive exposure to full agonists causes β_2-adrenergic desensitization; in contrast, exposure to partial agonists does not cause desensitization. Intrinsic efficacy may provide the rationale for the clinical use of β_2-adrenergic receptor agonists in asthma and COPD. In conclusion, the G protein/K_{Ca} linkage and intrinsic efficacy (allosteric effects) may be therapeutic targets for research and development of novel agents against both airway obstruction and airway remodeling.

Contents

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1. Introduction

Since the fundamental pathophysiology of asthma is eosinophilic infiltration of the airways, glucocorticosteroids are very effective for this disease. In contrast, since chronic obstructive pulmonary disease (COPD) is characterized by neutrophil inflammation in the airways, including oxidative stress and protease activity, there are no anti-inflammatory agents for COPD. β_2-adrenergic receptor agonists and muscarinic receptor antagonists are widely used as more effective bronchodilators for asthma and COPD to improve symptoms, to improve lung function, and to reduce the frequency and severity of exacerbations. Moreover, the combination of these two agents (dual bronchodilator therapy) in COPD may cause greater improvements in these clinical effects than each agent used alone (Bateman et al., 2013; Wedzicha et al., 2013).

Daily administration of azithromycin, a subclass of macrolide antibiotics, to patients with COPD shows efficacy against exacerbations, but this treatment is not recommended because of an unfavorable balance between benefits and adverse effects (Albert et al., 2011). Theophylline is less effective and less well tolerated than inhaled bronchodilators (β_2-adrenergic receptor agonists and muscarinic receptor antagonists) and is not recommended if the other agents are available and affordable. Leukotriene receptor antagonists inhibit leukotriene-induced contraction of airway smooth muscle; however, these agents are not used clinically as bronchodilators, because these agents are less potent as bronchodilators.

In the airway smooth muscle, responses to spasmogens, such as histamine, muscarinic receptor agonists, and leukotrienes, that act on trimeric G protein-coupled receptors (GPCRs), are involved in airflow limitation and airway hyperresponsiveness, which are implicated in the pathophysiology of asthma and COPD. A reduction in tension of airway smooth muscle via activation of β_2-adrenergic receptors and via inhibition of muscarinic receptors contributes to therapy for asthma and COPD. Recent clinical trials have shown glucocorticosteroids may be insufficient to prevent airway remodeling in asthma, which is due to migration and contraction of airway smooth muscle; bronchodilators such as β_2-adrenergic receptor agonists and muscarinic receptor antagonists are needed (Grainge et al., 2011; Kelly et al., 2010). Therefore, among bronchodilators, these agents may contribute not only to mechanical tone but also to remodeling in the airways.

The tone of airway smooth muscle is mediated by myosin light chain phosphorylation. This phosphorylation is regulated by both the activation of myosin light chain kinase, which is dependent on the concentrations of intracellular Ca^{2+} (Ca^{2+} dynamics), and the inactivation of myosin phosphatase, which is independent of the concentrations of intracellular Ca^{2+} (Ca^{2+} sensitization) (Kume, 2008). Contractile agonists acting on trimeric GPCRs activate receptor-operated Ca^{2+} influx and cause Ca^{2+} release from sarcoplasmic reticulum via the production of 1,4,5-triphosphate (IP_3). This Ca^{2+} release activates store-operated Ca^{2+} influx (Ito et al., 2002). Moreover, L-type voltage-dependent Ca^{2+} (VDC) channels are partly involved in the Ca^{2+} influx (Kume et al., 2003). Ca^{2+} dynamics (Ca^{2+}-dependent mechanisms) are mainly due to these pathways. On the other hand, these contractile agonists also activate RhoA, a monomeric G protein, mediated by activation of trimeric GPCRs. Rho-kinase activated by GTP-RhoA, which is the active form of RhoA, phosphorylates (inactivates) myosin phosphatase, and Rho-kinase may be involved in not only airway contraction, but also other aspects of the pathophysiology of asthma (Kume, 2008; Kume et al., 2007; Oguma et al., 2007; Takeda et al., 2006; Taki et al., 2007). Ca^{2+} sensitization (Ca^{2+}-independent mechanisms) is mainly due to this pathway. Ca^{2+} dynamics and Ca^{2+} sensitization play an important role in airway smooth muscle contraction induced by various factors (Ito et al., 2001, 2006; Ito et al., 2008; Kojima et al., 2007; Shiraki et al., 2009). However, little is known about the effects of these bronchodilators on Ca^{2+} signaling and their mechanisms.

Reductions in concentrations of intracellular Ca^{2+} and phosphorylation by cAMP-dependent protein kinase (protein kinase A: PKA) are mechanisms of β_2-adrenergic action on airway smooth muscle. β_2-adrenergic receptor agonists relax airway smooth muscle with reducing membrane potential (hyperpolarization) (Honda et al., 1986). Large-conductance Ca^{2+}-activated K^+ (K_{Ca}) channels are densely distributed on the surface of the cell membrane in airway smooth muscle (Kume et al., 1989, 1990; McCann & Welsh, 1986). Activation of these channels produces large outward currents, leading to hyperpolarization, and Ca^{2+} influx related to the membrane potential, such as that through VDC channels, is suppressed, leading to the relaxation of airway smooth muscle (Kume et al., 2003; Wang et al., 1997), similar to vascular smooth muscle (Brayden & Nelson, 1992). In pulmonary vessels, K_{Ca} channels serve as a brake on vasoconstriction (Bonnet & Archer, 2007; Gutman et al., 2005). Recently, hyperpolarization mediated by activation of K_{Ca} channels has been proposed as the mechanism underlying bitter tastant-induced relaxation of airway smooth muscle, although an alternative pathway may also be an explanation (Deshpande et al., 2010). K_{Ca} channels are regulated not only by PKA, but also by trimeric G proteins, which regulate adenylyl cyclase activity (Kume & Kotlikoff, 1991; Kume et al., 1989; Kume et al., 1992, 1994). Hence, Ca^{2+} dynamics due to K_{Ca} channel activity may contribute to airway smooth muscle tone (functional antagonisms) induced by β_2-adrenergic and muscarinic receptors. Ca^{2+} homeostasis may play an important role not only in tone, but also in remodeling of airway smooth muscle (Mahn et al., 2010). An antagonist of VDC channels reduces airway remodeling in patients with severe asthma (Girodet et al., 2015), suggesting that inhibition of VDC channels via K_{Ca} channel-induced hyperpolarization is involved in this phenomenon. Although the clinical relevance of K_{Ca} channels in airway smooth muscle is still unclear, the effects of the K_{Ca} channel may be not only reduction of bronchoconstriction, but also prevention of airway remodeling in asthma.

As characteristics of the interaction of β_2-adrenergic receptor agonists with their target receptors, parameters such as affinity, potency, and intrinsic efficacy (or intrinsic activity) have been proposed (Hanania et al., 2002). Intrinsic efficacy refers to the ability of an agent to activate its receptors without regard to concentration. Intrinsic efficacy of each agonist is expressed by differences between Kd (the dissociation constant: the dependency of receptor occupancy on agonist concentration) and EC_{50} (agonist concentration that produces 50% inhibition of the maximal contraction). Since a limited dose of β_2-adrenergic receptor agonists is inhaled as bronchodilator therapy, affinity for the receptors may be a relatively unimportant parameter in determining the clinical effects of these agonists. In clinical use, when β_2-adrenergic receptor agonists with higher EC_{50} values are inhaled, higher doses are needed to achieve a sufficient response as compared to agonists with lower EC_{50} values. Hence, potency may also be a relatively unimportant parameter in determining the clinical effects of these agonists. In contrast, intrinsic efficacy may reflect the capability of β_2-adrenergic receptor agonists to activate the receptors in clinical use. In the research and development of β_2-adrenergic receptor agonists, affinity and potency have been fully considered, while intrinsic efficacy has not been considered at all. International guidelines for the management of asthma and COPD have never addressed the intrinsic efficacy of these agents.

Airway smooth muscle is a therapeutic target for asthma and COPD. Research and development of bronchodilators are needed to identify proteins that converge in the functional antagonism between β_2-adrenergic and muscarinic actions. The present study was designed to examine the intracellular mechanisms underlying the effects of bronchodilators for clinical use with a focus on Ca^{2+} dynamics via the K_{Ca} channel/G proteins linkage, Ca^{2+} sensitization via RhoA/Rho-kinase processes, and intrinsic efficacy in airway smooth muscle for development of a novel agent that has effects on both airflow limitation and airway remodeling.