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ADENOSINE RECEPTORS AS TARGETS FOR THERAPEUTIC INTERVENTION IN ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Abstract

Asthma and chronic obstructive pulmonary disease (COPD) are pulmonary disorders characterized by various degrees of inflammation and tissue remodeling. Adenosine is a signaling molecule that is elevated in the lungs of patients with asthma and COPD. Adenosine elicits its actions by engaging cell surface adenosine receptors, and substantial preclinical evidence suggests that targeting these receptors will provide novel approaches for the treatment of asthma and COPD. Studies in animal models of airway disease suggest that there may be clinical benefit to the use of A₁, A₃ and A_{2B} adenosine receptor antagonists in the treatment of features of asthma and/or COPD, while A_{2A} agonists may also prove effective. Several adenosine receptor based pharmacologic agents have entered clinical development for the treatment of asthma and COPD; however, the studies have been limited and the efficacy of such approaches is not yet clear.

Keywords

respiratory diseases; COPD; asthma; fibrosis; G-Protein coupled receptors; inflammation

Introduction

Chronic airway diseases such as asthma and chronic obstructive pulmonary disease (COPD) are prevalent inflammatory disorders of the lung that are poorly managed, and for which few new drugs have been developed (see Text Box). Pharmaceutical companies and research institutions are addressing the substantial potential for the development of novel therapeutic agents that modulate adenosine signaling with significant clinical advantage for chronic inflammatory airway diseases [1].

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Extracellular adenosine levels are elevated in response to cellular stress and injury through pathways that involve the release of adenine nucleotides and their subsequent dephosphorylation to adenosine [2]. The production of extracellular adenine nucleotides and adenosine can regulate cell function by engaging purinergic type II or type I receptors respectively. This review will focus on the type I or adenosine receptors. These receptors are expressed on various inflammatory and stromal cells and have well characterized anti-inflammatory and wound healing activities that demonstrate the importance of these signalling pathways in tissue protection [3] (Figure 1). In some situations; however, adenosine generation and receptor engagement have pro-inflammatory and tissue destructive activities [4] that serve to amplify tissue injury (Figure 2). This appears to be the case with inflammatory lung diseases such as asthma and COPD. Much evidence suggests that adenosine is playing a detrimental role in these and perhaps other chronic disorders of the airways (Table 1). The observations summarized in Table 1 suggest that adenosine signaling has a potentially pathophysiological role in chronic inflammatory disorders of the airways. These important observations have driven research efforts to develop selective agonists or antagonists for adenosine receptor subtypes for use as novel therapies for asthma and COPD.

Here we review proposed mechanisms of action of adenosine receptors in preclinical studies and describe molecules with high affinity and selectivity for the human adenosine receptor subtypes that are under investigation at preclinical and clinical levels as treatments for respiratory diseases. Findings in preclinical studies suggest there may be efficacy in the use of A₁R, A₃R and A_{2B}R antagonists in the treatment of key features of asthma and COPD, while A_{2A}R agonist may prove beneficial as well. However, the results from clinical trials testing such hypotheses are limited and without firm conclusion.

Targeting adenosine receptor subtypes

Adenosine levels are elevated in the lungs of individuals with asthma and COPD, and adenosine receptors are known to be expressed on most if not all inflammatory and stromal cell types involved in the pathogenesis of these diseases. Extracellular adenosine elicits its effects by interacting with four receptors: A₁R, A_{2A}R, A_{2B}R and A₃R (Figure 1) [2]. These receptors are differentially expressed in the human lung [5]. The ability of adenosine, whose levels are raised in many pathophysiological conditions, to activate these four receptors varies depending on binding affinity, receptor density and the type of G protein involved [2]. In particular, A₁R and A_{2A}R can be activated by physiological levels of adenosine, whereas A_{2B}R and A₃R require higher concentrations of adenosine for their activation. Studies in animal model systems provide evidence that complex yet specific receptor responses exist and are driven by cell type and tissue specific expression of these receptors.

A₁R: Preclinical Studies

As with all of the adenosine receptors, there is evidence that A₁R exhibits both pro- and anti-inflammatory activities in cellular and animal models of inflammation [3]. In the context of models directed at human asthma, however, the preponderance of studies suggests that this receptor has a pro-inflammatory role. Attention was drawn to this receptor's role in asthma in studies demonstrating that treatment with A₁R antagonists [6] and antisense oligodeoxynucleotides [7] directed against A₁R could attenuate bronchoconstrictor responses in an allergic rabbit model. Whether these effects were mediated by blocking A₁R on airway smooth muscle, inflammatory cells or airway nerves is not clear; however, recent studies in A₁R knockout mice support the idea that a neuronal component is involved in adenosine-mediated bronchoconstriction [8]. More recent studies in the allergic rabbit model have demonstrated that treatment with an A₁R antagonist can attenuate pulmonary inflammation as well as bronchoconstriction [9]. Additional evidence supporting a role for A₁R in asthma is

the ability of this receptor to influence mucin production and secretion. A₁R signaling can enhance MUC2 mucin gene expression in human bronchial epithelial cells in vitro [10]. Lastly, A₁R levels are elevated in several preclinical models of chronic lung disease [11-14], and a recent study has demonstrated that A₁R levels are elevated in bronchial epithelial and airway smooth muscle cells of asthmatics [15]. Up-regulation of this receptor in asthma is supportive of a role for this signaling pathway in the pathophysiology of this disease.

Collectively, these preclinical studies build a compelling case that treatment with A₁R antagonist might provide an avenue for attenuating features of asthma including airway inflammation, mucus production and bronchoconstriction. There is evidence; however, that A₁R plays anti-inflammatory roles in the lungs of adenosine deaminase (ADA)-deficient mice (Table 2), [16]. ADA is the major enzyme that controls endogenous adenosine levels and consequently ADA-deficient mice develop progressive increases in lung adenosine in association with pulmonary inflammation and tissue remodeling [17,18]. Although this model is complex and its relevance to human asthma debatable, it does reveal the consequences of prolonged increases in adenosine on pulmonary inflammation, and it suggests that A₁R signaling might serve different functions at different disease stages. In general, there is still much that is not understood about the specific cellular mechanisms of this receptor in regulating the features of inflammation and airway pathophysiology seen in asthma. Continued research efforts in models of airway inflammation are warranted in this regard, but it is likely that the results of clinical trials utilizing A₁R antagonists will provide the most definitive pathway forward for understanding the role of this receptor in human airway disease.

A₁R: Clinical Trials

Elevated expression of A₁R has been reported in bronchial biopsy specimens obtained from asthmatic subjects [15], where immunoreactivity appears to be predominantly located in the bronchial epithelium and bronchial smooth muscle. Moreover, the methylxanthine bamiphylline might produce its anti-asthma effects in humans by blocking A₁R [19]. Given these findings, and given that activation of A₁R on human airway epithelial, bronchial smooth muscle cells, neutrophils, macrophages and fibroblasts (reviewed in [20]) induces the release of mediators and cytokines that lead to airway hyperreactivity, inflammation and airway remodeling, it is not surprising that several companies are pursuing this target in human asthma and COPD.

EPI-2010, a 21-mer antisense oligodeoxynucleotide targeting human A₁R, has been tested as an anti-asthma drug. In a small clinical trial conducted in patients with asthma, a single dose of EPI-2010 reduced the need for bronchodilator drugs to control asthma symptoms, concomitant with a reduction in asthma symptom scores [21]. This effect was statistically and clinically significant and lasted for one week following a single dose. Because of disappointing results in a Phase II clinical trial, EPI-2010 was discontinued from clinical testing [22]; however, because of safety concerns with the use of antisense oligonucleotides as therapeutics in humans, it is possible that the doses of EPI-2010 used were sub-therapeutic in this study.

Another potential agent, currently in preclinical development as a once daily oral treatment for human asthma, is L-97-1, a small-molecule A₁R antagonist [19]. As compared with bamiphylline, L-97-1 has a considerably higher affinity and selectivity for human A₁R [19]. In a rabbit model of allergic asthma, L-97-1 blocks allergic airway responses, airway hyperresponsiveness to histamine, and airway inflammation [9,19].

A_{2A}R: Preclinical Studies

Increasing evidence suggest that A_{2A}R mediates potent anti-inflammatory activities on specific cells and in various models of inflammation, which has promoted the development of A_{2A}R

agonists for the attenuation of inflammation in many disorders (reviewed in [3]). Given the central role of inflammation in asthma and COPD, there has been substantial preclinical research activity targeted at understanding the function of A_{2A}R in models of airway inflammation.

Among the earliest, was a study by Fozard and colleagues demonstrating that intra-tracheal treatment with A_{2A}R agonist CGS21680 inhibits airway inflammation in allergen sensitized and challenged brown Norway rats [23]. Similar findings were reported in a mouse model of ovalbumin sensitization and challenge where CGS21680 treatment inhibited inflammatory cell recruitment in the lavage fluid [24]. Interestingly, differences in mucus secretion and airway hyperresponsiveness were not seen. The same study demonstrated mixed effects of A_{2A}R agonist treatment on the airway inflammation seen after exposure to LPS or cigarette smoke. Consistent with these findings, A_{2A}R knockout mice that have been sensitized and challenged with ragweed exhibit enhanced airway inflammation and airway hyperresponsiveness as compared with wild-type mice [14]. In addition, a recent study in ADA-deficient model demonstrated that genetic removal of A_{2A}R leads to enhanced pulmonary inflammation, mucus production and alveolar airway destruction [25], (Table 2) further implicating A_{2A}R signaling pathways as important anti-inflammatory networks in the lung. However, recent studies have described the ability of A_{2A}R activation to promote fibrosis [26], suggesting there may be side effects associated with persistent A_{2A}R activation.

A_{2A}R: Clinical Trials

Detailed characterization of the immunohistochemistry and binding of A_{2A}R in human lung parenchyma of patients with COPD has revealed the presence of this receptor subtype in bronchiolar and alveolar epithelial cells, bronchiolar smooth muscle cells and endothelial cells with a high affinity and density [5]. Because activation of A_{2A}R increases intracellular cAMP similar to other agents that increase intracellular cAMP, *e.g.* PDE-IV inhibitors, beta-2 agonists or theophylline, A_{2A}R agonists may represent a new class of anti-asthma drugs that produce bronchodilation and anti-inflammatory effects. Thus, selective A_{2A}R agonists may also provide an alternative to corticosteroids for the treatment of airway inflammatory diseases.

Unfortunately, administration of the selective A_{2A}R agonist GW328267X by inhalation at a dose of 25 µg twice daily, in 15 nonsmoking atopic asthmatics in a double-blind, placebo and fluticasone propionate (250 µg) controlled study, failed to protect against allergen-induced early or late asthmatic reactions, or the associated inflammatory response in the induced sputum [27]. An obvious explanation is that the dose of the drug used was sub-therapeutic as suggested by the lack of adverse effects at a cardiovascular level. By increasing intracellular cAMP, activation of A_{2A}R may also produce the cardiovascular side effects of hypotension and reflex tachycardia [28]; a factor that is likely to substantially reduce the therapeutic index of A_{2A}R agonists as drug candidates in humans. GlaxoSmithKline has discontinued the clinical development of GW328267X. Conversely, the adenosine A_{2A}R agonist UK371,104 is beneficial in the lung of anaesthetized guinea-pigs without any obvious cardiovascular side effects and may be valuable to explore the anti-inflammatory potential of inhaled adenosine A_{2A}R agonists in clinical trials [29]. UK432,097 is an analogue of UK371,104 with a similar lung focus of pharmacological activity in the anaesthetized guinea pig model discussed above. UK432,097 is currently in phase II trials for COPD [29].

A_{2B}R: Preclinical Studies

The A_{2B}R has the lowest affinity for adenosine, yet this receptor might be important in pathological environments where adenosine levels are elevated such as asthma [30]. In support of this, multiple studies demonstrate the ability of A_{2B}R engagement to promote the expression of pro-inflammatory mediators from various cell types critical to processes seen in chronic

lung diseases. This includes the release of IL-8 from HMC-1 cells [31], IL-4 and IL-13 [32, 33] from HMC-1 cells and mouse bone-marrow-derived mast cells, IL-19 from airway epithelial cells [34] and MCP-1 from bronchial smooth muscle cells [35]. In addition, A_{2B}R activation promotes the production and release of IL-6 from airway epithelial cells [36], macrophages [37], pulmonary fibroblasts [38] and bronchial smooth muscle cells [35].

Adenosine potentiates the release of preformed mediators from sensitized mast cells, which is thought to be the underlying mechanism by which adenosine provocation elicits bronchoconstriction in asthmatics [30,39]. The A_{2B}R has been suggested to orchestrate key responses to adenosine in several respiratory conditions in humans, but direct evidence demonstrating the expression of this receptor on mast cells in the lung, or the existence of specific A_{2B}R responses, is scarce in the literature. Studies utilizing antagonists and knockout mice suggest that the degranulation of mast cells in rodents is mediated through A₃R [40,41]; moreover, examination of isolated mast cells from A_{2B}R knockout mice suggest this receptor is not involved in the degranulation process [42], but is important in promoting the production of IL-4 and IL-13 from these cells [33], which may affect late-stage or chronic features of airway diseases such as asthma. Thus, adenosine probably elicits important responses on mast cells that can influence acute and chronic features of asthma; however, additional studies are needed to more precisely define the specific adenosine receptors responsible for such activities on human mast cells.

A recent study revealed that treatment with A_{2B}R antagonist CVT-6883 attenuated airway inflammation and airway hyperreactivity in a mouse model of ragweed sensitization and challenge [43]. In addition, work in the ADA-deficient model suggests that A_{2B}R signaling engages pathways that promote chronic airway inflammation and remodeling (Table 2) [44]. Noted features include the accumulation of activated alveolar macrophages, airspace destruction, mucus cell metaplasia and pulmonary fibrosis. A_{2B}R expression is elevated in the lungs of ADA-deficient mice and treatment of these mice with the selective A_{2B}R antagonist CVT-6883 results in decreased production of pro-inflammatory mediators in association with diminished airspace enlargement and pulmonary fibrosis [44]. Consistent with this is the observation that adenosine and A_{2B}R levels are elevated in the lungs of IL-13 [12] and IL-4 [13] over expressing mice that develop pathological features of asthma, COPD and pulmonary fibrosis. Moreover, increases in A_{2B}R have recently been described as a distinguishing feature of individuals with accelerated pulmonary fibrosis [45]. Additional studies supporting a pro-fibrotic role for A_{2B}R signaling include the demonstration that activation of A_{2B}R can promote the differentiation of human pulmonary fibroblast into collagen-producing myofibroblasts [38], and engagement of A_{2B}R can directly up-regulate the production of the pro-fibrotic molecule fibronectin in alveolar epithelial cells [46]. The demonstration that adenosine can directly promote these processes, further strengthens the likelihood that this nucleoside is in itself pro-fibrotic and strongly implicates A_{2B}R as a pro-fibrotic receptor. These studies suggest that up-regulation and engagement of A_{2B}R might serve to enhance chronic remodeling in lung diseases.

These preclinical data suggests that A_{2B}R antagonists may have utility in the treatment of chronic lung diseases where fibrosis is a major component, including the airway remodeling seen in asthma and in patients with interstitial lung diseases where fibrosis is detrimental. It must be realized, however, that A_{2B}R signaling also serves important anti-inflammatory functions in acute lung injury that might make the timing of A_{2B}R antagonist treatment important [47]. In addition, A_{2B}R expressed on airway epithelial cells has been implicated in the regulation of airway surface liquid volume mucous clearance [48]. Disruption of these features should therefore be monitored closely as a side-effect of A_{2B}R antagonist usage in the lungs.

A_{2B}R: Clinical Trials

Characterization of human lung parenchyma in patients with chronic inflammation of the airways suggests that A_{2B}R might be present on mast cells and macrophages [5]. As compared with control smokers, the affinity and density of these receptors in COPD patients appears to be substantially modified, suggesting adenosine signalling may be important in COPD. Such a role for A_{2B}R signalling in the pathophysiology of asthma receives support from pharmacological studies using the adenosine receptor antagonists theophylline and enprophylline [49]. Though these agents can inhibit phosphodiesterase activity at high concentrations, the affective therapeutic concentrations used to improve lung function and symptoms in subjects with asthma were relatively low and in the range of their A_{2B}R affinities [50].

The potent and highly selective A_{2B}R antagonist CVT 6883 has completed Phase 1 clinical trials with no adverse events reported and has entered Phase 2 trials for human asthma [51]. This compound is stated to have an A_{2B}R K_i = 8nM with at least 1000-fold selectivity against the other adenosine receptors [44]. Finally, Novartis has recently reported that their aminothiazole dual A_{2B}R/A₃R antagonist, QAF 805, failed to attenuate bronchial hyperresponsiveness to inhaled AMP in a placebo controlled, double-blind, randomized, two-way crossover Phase 1b clinical trial of 24 AMP-sensitive asthmatics [52].

A₃R: Preclinical Studies

The A₃R plays complex roles in inflammation, with both pro- and anti-inflammatory functions being described in multiple cellular and animal models with varying roles being dictated largely by species differences (for review see [53]). This receptor has also received attention in chronic inflammatory disorders of the airways. Transcript levels of A₃R are elevated in lung biopsies of patients with asthma or COPD [54], where it is thought to localize to eosinophils. Functions attributed to A₃R activation on human eosinophils include the inhibition of chemokine-induced migration [54] and the inhibition of degranulation and superoxide anion release [55], suggesting A₃R agonists might have utility in the treatment of asthma.

In contrast to these findings in humans, pre-clinical studies in animal models suggest that A₃R has a pro-inflammatory role in chronic inflammatory diseases of the airways. A₃R is abundantly expressed on mouse eosinophils [56], and in vitro studies with mouse eosinophils confirm a role for this receptor in chemokine-induced eosinophil migration [56]. However, genetic removal or pharmacological blockade of A₃R in ADA-deficient mice results in decreased airway eosinophilia, but does not affect the degree of circulating eosinophilia, suggesting that A₃R signaling is important in eosinophil trafficking in this model (Table 2). Moreover, a recent study demonstrated the absence of eosinophil peroxidase in the airways of A₃R-deficient mice exposed to fibrosis inducing agent, bleomycin [57], suggesting that this receptor is needed for eosinophil degranulation in vivo. A₃R is also abundant on rodent mast cells and is responsible for adenosine-mediated mast cell degranulation in vitro and in vivo in multiple models [40,41]. In addition, A₃R is markedly elevated in mucin-producing bronchial airway epithelial cells in several models of Th2-mediated airway inflammation and airway remodeling [12,56,58], and evidence from A₃R over expressing and knockout mice suggests that this receptor serves to enhance mucus secretion in these environments [58]. These findings suggest that treatment with A₃R antagonists might have benefit in models of allergic airway inflammation. The discrepancies between findings in human cellular systems and those in animal models might be due to species differences or the inability to adequately assess the function of A₃R in vivo in humans. It is likely that the usefulness of A₃R agonists and antagonists in the treatment of asthma and COPD will only be revealed following appropriate clinical trials with such compounds.

A₃R: Clinical Trials

As mentioned above, transcript levels of A₃R are elevated in lung biopsies of patients with asthma or COPD where it appears to be involved in the inhibition of eosinophil chemotaxis. Because asthmatic inflammation is characterized by extensive infiltration of the airways by activated eosinophils, elevated adenosine concentrations associated with asthma may contribute to eosinophilic trafficking through modulation of A₃R. King Pharmaceuticals published a patent application claiming a particularly potent and selective A₃R antagonist for asthma characterized by a tricyclic xanthine derivative structure [59]. As mentioned above, a dual A_{2B}R/A₃R antagonist, QAF 805 from Novartis failed to attenuate bronchial hyperresponsiveness to inhaled AMP in a placebo controlled, double-blind, randomized, two-way crossover Phase Ib study of AMP-sensitive asthmatics [52].

Conclusions

The pharmacological arsenal for allergy and asthma is fast growing, and significant endeavors in medicinal chemistry and pharmacology have yielded a number of safer and highly selective compounds directed against the four known adenosine receptor subtypes. Some of these compounds have entered clinical development and may be of assistance in the process of finding better therapies for patients with asthma and COPD (Table 3).

Although adenosine generation and the subsequent engagement of adenosine receptors on inflammatory and pulmonary cells appears to play an important pathogenetic role in regulating chronic lung disorders such as asthma and COPD (Figure 2), this knowledge has not yet been translated into effective treatments [60]. It is likely that this failure reflects our limited comprehension of the complex interplay driven by the different pattern of receptor distribution and/or affinity of the four known adenosine receptor subtypes in specific cell types at different stages of the disease. Consequently, a complete and full characterization of adenosine receptor subtype distribution in the airways and their specific role in the response to adenosine in health and disease is mandatory. With this information, attempts at elucidating the role of specific adenosine receptors as valuable therapeutic targets in asthma and COPD may be conclusive.

Text Box Asthma and COPD

Asthma is a chronic inflammatory disease of the airways characterized by some degree of mast cell and eosinophilic airway infiltration/activation driven by specific cytokines and chemokines produced by CD4⁺ Th2 lymphocytes [61]. Clinically, asthma is characterized by the sudden onset or deterioration of wheezing, cough, dyspnea, mucous production and concomitant airway obstruction in response to exposure to various stimuli. Asthma in most patients can be controlled by regular use of anti-inflammatory (i.e. inhaled corticosteroids) and bronchodilator maintenance agents (i.e. inhaled β 2-agonists). Nonetheless, for some patients asthma continues to be poorly controlled in terms of ongoing symptoms, frequent exacerbations, persistent and variable airway obstruction, and frequent requirement for β 2-agonists despite aggressive treatment.

In chronic obstructive pulmonary disease (COPD), the persistent inflammatory response of the airways is typically associated with smoking [62]. This response cannot be reversed and generally leads to progressive airflow limitation, impairment of gas exchange, respiratory failure, cor pulmonale and death. The inflammatory infiltrate of COPD is distinct from that of asthma, with neutrophils, macrophages and CD8⁺ T-lymphocytes in small and large airways, as well as in lung parenchyma and pulmonary vasculature. For individuals whose asthma or COPD is not adequately controlled with conventional treatments, a few additional therapies, including methylxanthines, anticholinergics, cromones and leukotriene modifiers, are available but have variable efficacy. Consequently, there is a compelling need

for improved therapeutic strategies for these individuals, particularly oral therapies that enhance patient compliance.

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Figure 1.

Adenosine signaling. Adenosine binding to A₁R and A₃R results in the inhibition of adenylate cyclase (AC) with an overall reduction in cyclic AMP (cAMP). The canonical signaling mechanism of adenosine A_{2A}R and A_{2B}R is the stimulation of AC, followed by an increase in cAMP levels via coupling to stimulatory G proteins (G_s). However, adenosine A_{2B}R and A₃R can, in addition, elevate inositol (1,4,5)-trisphosphate (IP₃) levels via G_q activation. Ligand interaction with A₁R, A_{2A}R, A_{2B}R and A₃R expressed on inflammatory and stromal cells types in the lung elicits effects relevant to the pathogenesis of asthma and COPD and all are potential targets for drug development. Many studies of models directed at human asthma and COPD suggest that A₁R has a pro-inflammatory role. Activation of A₁R can also elicit bronchoconstriction and increase mucin secretion. A_{2A}R mediates potent anti-inflammatory activities on specific cells and in various models of inflammation including asthma and COPD. Activation of A_{2A}R can also elicit bronchodilation in animal models of asthma; however, the potential effects of A_{2A}R activation in enhancing fibroproliferation and excessive matrix deposition in the airways can be detrimental. A_{2B}R engagement promotes the release of pro-inflammatory mediators and cytokines from various cell types critical to processes seen in chronic lung diseases. Some of these mediators such as histamine and prostaglandins are also potent bronchoconstrictors in asthma and COPD. Others such as CXCL1, TGF-β1 and osteopontin appear to be associated with alveolar airway destruction, mucous cell metaplasia and pulmonary fibrosis. Activation of A₃R plays complex roles in inflammation, with pro- and anti-inflammatory effects depending largely on species differences. In rodents, A₃R signaling appears to be important in eosinophil trafficking and activation and in mast cell degranulation.

Figure 2.

Proposed model of adenosine-mediated amplification of asthma and chronic obstructive pulmonary disease (COPD). Several triggers and cellular mediators can lead to the development of asthma and COPD. Exogenous and endogenous triggers can raise extracellular adenosine levels in response to tissue damage and inflammation through pathways that involve the release of adenine nucleotides and their subsequent dephosphorylation to adenosine. Although physiological levels of extracellular adenosine might be important in the resolution of inflammation or tissue repair by activation of high-affinity adenosine receptors, elevated levels of adenosine may lead to the exacerbation of lung inflammation and damage through the activation of low-affinity adenosine receptors such as A_{2B}R.

Table 1

Evidence for a pathophysiological role for adenosine signaling in chronic inflammatory disorders of the airways in man [30,39]

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1	elevated levels of adenosine have been detected in the plasma, lavage fluid and EBC of patients with asthma and COPD, and in animal models that exhibit features of chronic airway disease
2	aerosol adenosine exposure induces a dose-related bronchoconstriction in patients with asthma and COPD but not in normal controls
3	non selective adenosine receptor antagonists (i.e. theophylline, enprophylline and bamiphylline) improve lung function and symptoms in asthma and COPD
4	engagement of adenosine receptors on numerous inflammatory and stromal cells types central to asthma and COPD have been shown to elicit pro-inflammatory responses
5	airways responses to AMP more closely reflects an inflammatory process and the phenotype for human allergic asthma than does sensitivity to other known agonists
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Table 2

Function of adenosine receptors in adenosine mediated lung injury in ADA-deficient mice.

A₁R Signaling Reduces/Enhances	A_{2A}R Signaling Reduces	A_{2B}R Signaling Enhances	A₃R Signaling Enhances
inflammation	inflammation	inflammation	inflammation
Th2 cytokine production	mucus metaplasia	Th2 cytokine production	eosinophil trafficking
mucus metaplasia	angiogenesis	protease-mediated airway destruction	mast cell degranulation
protease-mediated airway destruction		fibrosis	mucus metaplasia and secretion

Pharmacological blockade and/or genetic removal of the various adenosine receptors from ADA-deficient mice has provided insight into the role of these receptors in pulmonary environments exposed to high levels of adenosine for a prolonged period.

Table 3

Adenosine receptor agonists and antagonists in clinical development for asthma and/or COPD

Drug Name	Molecular Targets	Clinical Indication	Status
EPI-2010 (EpiGenesis Pharmaceuticals)	antisense oligonucleotide of A ₁ AR	inhibition of BHR and bronchodilatation	discontinued
UK-432,097 (Pfizer)	A _{2A} AR agonist	anti-inflammation	Phase 2
GW328267 (GSK)	A _{2A} AR agonist	anti-inflammation	discontinued
CVT-6883 (Cardiovascular Therapeutics)	A _{2B} AR antagonist	inhibitor of BHR and anti-inflammation	Phase 2
QAF 805 (Novartis)	Mixed A _{2B} / A ₃ AR antagonist	inhibition of BHR and anti-inflammation	Phase 1b