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REVIEW

Adenosine-receptor subtypes: their relevance to adenosine-mediated responses in asthma and chronic obstructive pulmonary disease

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Adenosine-receptor subtypes: their relevance to adenosine-mediated responses in asthma and chronic obstructive pulmonary disease. R. Polosa. ©ERS Journals Ltd 2002.

ABSTRACT: Adenosine administration by inhalation elicits concentration-related bronchoconstriction in subjects with asthma and chronic obstructive pulmonary disease (COPD). The mechanisms of adenosine-induced bronchoconstriction appear to involve a selective interaction with activated mast cells with subsequent release of preformed and newly-formed mediators. Further evidence linking adenosine signalling to asthma and COPD comes from the finding that many cell types that play important roles in the exacerbation of these conditions express adenosine receptors and demonstrate relevant effects through stimulation of these receptors.

Therefore, blockade of these receptors may be a valuable approach to the treatment of asthma and chronic obstructive pulmonary disease. Promising adenosine-receptor targets for novel therapeutics of asthma and chronic obstructive pulmonary disease have recently been identified in a number of inflammatory cell types, including mast cells, eosinophils, lymphocytes, neutrophils, and macrophages. The recent characterisation of the A_{2B} receptors indicates the human lung mast cell as one of the most strategic cellular targets.

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Adenosine has been suggested to play a role in inflammatory airway diseases such as asthma and chronic obstructive pulmonary disease (COPD) [1–3]. Elevated levels of adenosine have been measured in the airway lining fluid of patients with asthma and COPD when compared to normal controls [4]. In sensitised rabbits, high concentrations of adenosine have been reported in the lung-lavage fluid after allergen challenge [5], whereas in transgenic mice, adenosine-receptor transcripts are increased in association with lung inflammation and increased airways hyperresponsiveness [6]. Adenosine administration by inhalation elicits concentration-related bronchoconstriction in subjects with asthma and COPD [7, 8], whereas the nucleoside has no discernable effect on airway calibre in normal individuals. Since these initial observations were made, considerable effort has been directed toward revealing the fine mechanisms of adenosine-induced bronchoconstriction; these appear to involve a selective interaction with activated mast cells, with subsequent release of preformed and newly-formed mediators [9–13] (fig. 1).

There is now increasing evidence that evaluation of airway responsiveness by adenosine-induced bronchoconstriction may be valuable in differentiating asthma from COPD, monitoring anti-inflammatory therapy in asthma, surveying disease progression, and assessing disease activity in relation to allergic airway inflammation. In particular, adenosine responsiveness is closely associated with allergic airway inflammation, as recently demonstrated in studies of subjects

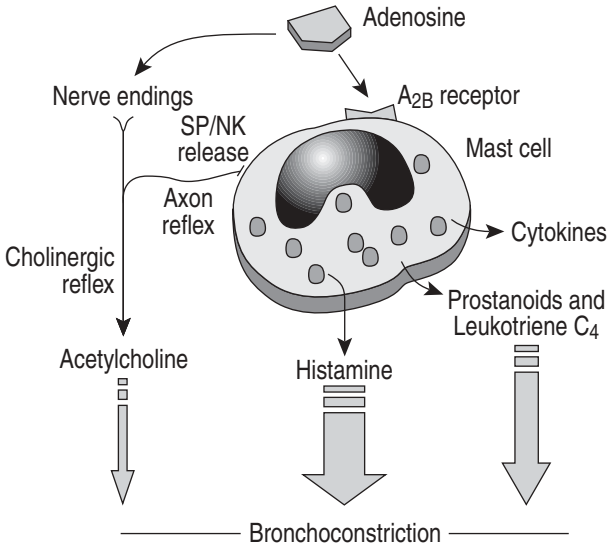

Fig. 1.–Proposed mechanisms by which adenosine cause bronchoconstriction in asthma and chronic obstructive pulmonary disease. Please note that mast-cell derived mediators are largely implicated in the airway response to adenosine (largest arrow), whereas the role of neural pathways is negligible (smallest arrow). SP: substance P; NK: neurokinins.

with asthma and active allergic rhinitis, in which airways responsiveness to adenosine 5′-monophosphate (AMP), but not methacholine, was strongly correlated with sputum eosinophilia [14, 15].

Further evidence linking adenosine signalling to asthma and COPD is provided by the finding that many cell types that play important roles in the exacerbation of these conditions, express adenosine receptors and demonstrate relevant effects through stimulation of these receptors. These include mast cells [16, 17], eosinophils [18], lymphocytes [19], neutrophils [20], and macrophages [21, 22].

In this article, evidence of a pathophysiological role of adenosine-receptor signalling in chronic inflammatory airway diseases, such as asthma and COPD, is reviewed.

Cellular mechanisms of adenosine-induced bronchoconstriction in asthma and COPD

Even if adenosine signalling is likely to involve many cell types with demonstrated relevant effects in asthma and COPD, only in recent times the bronchoconstrictor response that follows adenosine inhalation has attracted the attention of researchers in respiratory pharmacology and physiology. To date there are no adenosine antagonists that have been accepted for use in humans, but alternative pharmacological approaches have suggested that it is unlikely that adenosine acts directly on smooth muscle cells *in vivo*, but indirectly through activation of purinoreceptors expressed on intermediary inflammatory cells, such as mast cells, or on afferent nerve endings (fig. 1).

Neural pathways

Activation of neural pathways is suspected to contribute to the contractile airway response to adenosine. The possibility of a reflex cholinergic component was originally indicated by data from studies in inbred rats [23] and later confirmed in a clinical investigation in which premedication with high doses of the anticholinergic drug ipratropium bromide administered by inhalation significantly attenuated the bronchoconstrictor response to AMP in asthma [24]. Further support for a neural contribution to AMP-induced bronchoconstriction comes from observations made with frusemide and bumetanide, two loop diuretics that are also likely to act by modulating sensory nerve responses in the airways [25]. Inhalation of these drugs substantially inhibits the bronchoconstrictor response of AMP without affecting the response to histamine [26–28]. In guinea pigs *in vivo* the synthetic adenosine analogue, 2-chloroadenosine, provoked bronchoconstriction that was attenuated by capsaicin [29]. Moreover, in BDE rats, adenosine elicits increased pulmonary resistance by stimulating neuropeptide-producing nerves *via* prior mast-cell activation [30]. These observations indicate that the release of contractile neuropeptides from sensory nerve endings might be of some importance in mediating the airway effects of purine derivates. In order to probe this hypothesis, a protocol of repeated bradykinin bronchoprovocations as a model of neuropeptide depletion in humans was used. Repeated challenge with bradykinin, sufficient to cause a 15-fold reduction in response to the kinin, results in some attenuation of a subsequent AMP response, without affecting airway responsiveness to histamine [31]. However, inhibition of neutral endopeptidase (NEP) by inhaled phosphoramidon failed to elicit any significant enhancement of the bronchospastic response provoked by AMP, suggesting that release of endogenous neuropeptides has little importance in the airway response to adenosine [32]. The role of neural pathway in adenosine-induced bronchoconstriction in COPD patients has not been fully addressed. However, a recent study by REUTGERS *et al.* [33] showed no significant effect on AMP responsiveness after inhaled ipratropium bromide in patients with COPD, implying that vagal-nerve activation does not play a role. This contrasts with the findings in asthmatic patients, where ipratropium bromide caused an ~2.5-fold increase in the provocative concentration of AMP causing a 20% fall in the forced expiratory volume in one second (PC20) [24]. It is possible that in asthma, AMP stimulates mast cells to release histamine, which causes an additive effect *via* vagal-nerve stimulation. In COPD, histamine release may be smaller and inadequate for the stimulation of vagal-nerve endings during AMP challenge.

Mast cells

The fact that mast cells are likely to play a major role in the bronchoconstrictor response to inhaled adenosine, both in asthma and in the active inflammatory phase of COPD, is indicated by *in vitro* studies in which adenosine markedly enhances the release of histamine and other newly-formed spasmogens from human lung mast cells obtained by enzymatic dispersion [34, 35] and bronchoalveolar lavage [36]. Taken together, the above evidence indicates that the mast cell may be involved in the bronchoconstrictor response to inhaled adenosine, principally *via* release of granule-derived preformed mediators. What *in vivo* evidence is there to support this? In asthma, the mast-cell inhibitors, sodium cromoglycate, nedocromil sodium and salbutamol have been found to attenuate AMP-induced bronchoconstriction to a greater extent than bronchoprovocation provoked by the smooth-muscle agonist, methacholine [37, 38]. In addition, premedication with the potent H_1-histamine receptor antagonists, terfenadine and astemizole, has been shown to inhibit the acute bronchoconstrictor response to inhaled AMP in asthmatic and COPD patients [33, 39, 40]. More direct evidence that histamine released from airway mast cells are critical for adenosine-induced responses has come from work in which direct instillation of AMP into asthmatic bronchi [10] or into the nose of patients with allergic rhinitis [12] resulted in significant increases in the concentration of histamine and tryptase in their lavage fluid.

Since H_1-histamine receptor antagonists do not completely inhibit AMP-induced bronchoconstriction,

the role of other mast-cell derived mediators has to be considered. In addition to preformed mediators, the role of other mast cell-derived mediators has to be considered. The role of prostanoids in the response to AMP is supported by the demonstration that potent cyclo-oxygenase inhibitors, such as indomethacin and flurbiprofen, attenuate the constrictor effect of the nucleotide [9, 41]. In addition, lysine aspirin administered by inhalation causes some attenuation of the AMP response [11]. More direct evidence of the role of newly-generated mediators has come from the study by POLOSA *et al.* [10]. In addition to the rise in histamine and tryptase levels in the bronchoalveolar lavage fluid, an even greater increase in the prostaglandin D_2 (PGD_2) concentrations was found. Recently, premedication with Abbott's (ABT-761) [42], a potent 5-lipoxygenase inhibitor, and the selective cysteinyl leukotriene receptor 1 (Cys LT_1) receptor antagonist montelukast [13], has been shown to attenuate the acute bronchoconstrictor response to inhaled AMP, thus suggesting a role for spasmogenic leukotrienes.

These studies reasonably support the concept that mast-cell derived mediators are largely implicated in the bronchoconstrictor response to adenosine in asthma and COPD, which is probably the result of an interaction of the nucleoside with specific mast-cell surface receptors (fig. 1). However, the specific mast-cell adenosine-receptor subtype involved in the response is not known.

Adenosine metabolic pathways

Adenosine is a nucleoside consisting of the purine base, adenine, in glycosidic linkage with the sugar, ribose. Most extracellular adenosine derives from the enzymatic cleavage of the nucleotide AMP by a plasma membrane 5′-nucleotidase [43] (fig. 2). Although some of this AMP is generated from extracellular adenosine triphosphate (ATP), most is probably derived from intracellular AMP as it diffuses down its concentration gradient out of the cell and thereby encounters the 5′-nucleotidase located in the cell membrane. Intracellular AMP is mainly derived from the cleavage of adenosine diphosphate (ADP) and ATP during energy generation. Other pathways for the production of AMP do exist, but are quantitatively much less important. Although most intracellular AMP is normally reconverted to ADP and ATP, under conditions of high energy demand and/or hypoxia it is metabolised to adenosine by 5′-nucleotidase [44]. This may occur during inflammation when a large number of infiltrating inflammatory cells compete for a limited oxygen supply. Intracellular levels of adenosine are kept low principally by conversion to AMP by the enzyme adenosine kinase [45], but when energy demands are greater adenosine is also degraded to inosine and hypoxanthine by adenosine deaminase [46]. Extracellular adenosine diffuses back into the cell through the operation of an energy-independent nucleoside transporter [47]. Since intracellular adenosine levels are kept low, there is an inwardly directed concentration gradient (fig. 2).

Adenosine-receptor subtypes: a historical perspective

Once it is generated, extracellular adenosine elicits a variety of cellular responses relevant to asthma and COPD that are mostly mediated through interaction with G-protein coupled receptors on the surface

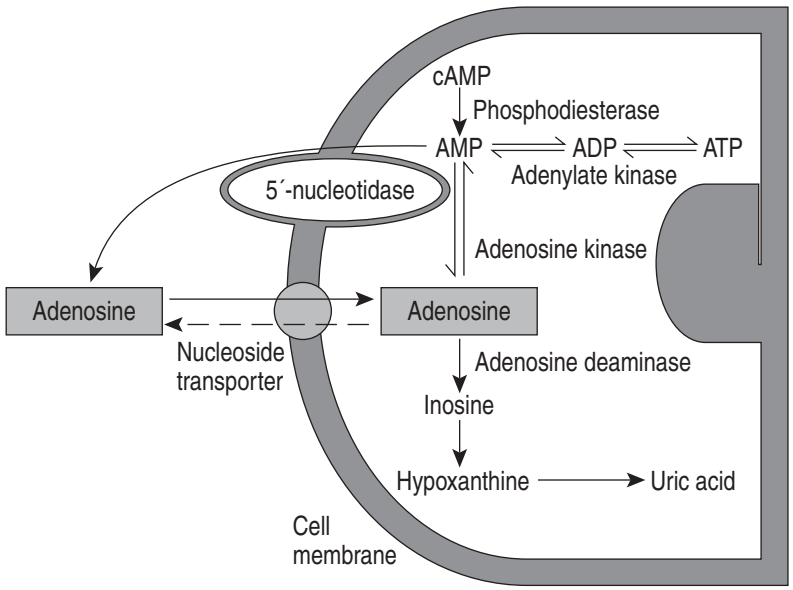

Fig. 2. – During the catabolism of high energy adenosine phosphates (adenosine triphosphate (ATP), adenosine diphosphate (ADP)), intracellular adenosine 5′-monophosphate (AMP) is formed and shortly reconverted to ADP and ATP as part of the energy cycle. However, under conditions of high-energy demand, AMP cannot be reconverted and it is metabolised to adenosine by a plasma membrane 5′-nucleotidase. Intracellular levels of adenosine are kept low principally by its conversion to AMP by the enzyme adenosine kinase, but when energy demands are greater, adenosine is also degraded to inosine and hypoxanthine by adenosine deaminase. Extracellular adenosine diffuses back into the cell through the operation of an energy-independent nucleoside transporter. cAMP: cyclic AMP.

of target cells [48]. The ability of the adenosine-uptake inhibitor, dipyridamole, to enhance adenosine-induced effects led to the suggestion that its actions are likely to be mediated through stimulation of specific receptors located on the cell surface [49, 50]. In addition, theophylline, a drug that is frequently used for resolution of airway obstruction in asthma and COPD, is known to attenuate adenosine-induced bronchoconstriction through an adenosine receptor antagonistic activity at therapeutic plasma levels (20–120 μM). In the early 1980s, understanding of adenosine receptors was simply based on the activity of "specific" agonists/antagonists and limited to a division between A_1 receptors (which decreased intracellular cyclic AMP (cAMP) levels) and A_2 receptors (which increased intracellular cAMP) [51, 52]. Suggestions that the adenosine A_1 receptor antagonistic activity of theophylline might explain its clinical potency received a blow when it was discovered that another xanthine, enprofylline, was just as effective as theophylline clinically but lacked adenosine A_1-receptor antagonistic activity. Enprofylline was also able to block adenosine-induced bronchospasm in asthmatic subjects and, despite its lack of A_1 receptor antagonistic activity, was more potent in this respect than theophylline. This paradox was at that time considered to be evidence against adenosine-receptor antagonism as an explanation of the clinical efficacy of xanthines. In the 1990s, information about new adenosine-receptor subtypes provided a possible explanation for the "enprofylline paradox". The application of molecular cloning techniques has expanded the range of known adenosine receptors to include the A_3 receptor [53] and the A_{2B} receptor (the originally described A_2 receptor now being designated A_{2A}) [54]. Enprofylline (as well as theophylline) inhibited ligand binding to the human recombinant adenosine A_{2B} receptor with a Ki of ~7 μM [55, 56], a value which lies well within the typical plasma levels of enprofylline after therapeutic dosage (5–25 μM). The stable adenosine analogue 5′-N-ethylcarboxamidoadenosine (NECA)-induced release of interleukin (IL)-8 from the human mast-cell line HMC-1, which appeared to be predominantly mediated over the A_{2B} receptor [57], was blocked by enprofylline, although the reported study did use a relatively high concentration of the drug (300 μM) [58]. Theophylline was also shown to block NECA-induced cAMP accumulation in Chinese hamster ovary (CHO) cells transfected with human A_{2B} receptors with a Ki of just <7 μM [59]. However, the fact that enprofylline has little affinity with the A_1 receptor does not mean that the A_1 receptor has no role in asthma. Indeed, an antisense oligonucleotide against the adenosine A_1 receptor is under investigation for just this purpose [60].

A detailed characterisation of adenosine-receptor subtypes has been conducted in human lung tissue and isolated human bronchoalveolar lavage cells in an attempt to define their pharmacological role in adenosine-induced responses. However, the limited specificity of available adenosine-receptor agonists and antagonists [48, 59, 61] makes identifying the adenosine-receptor subtypes involved a difficult task. Fortunately, however, antibodies or *in situ* hybridisation probes have recently become available for the different human adenosine-receptor subtypes. These studies can provide a more certain identification of receptor subtype as well as information on localisation.

Adenosine A_1 receptors

Description of adenosine A_1-receptor expression and distribution has been widely carried out in mammals. Binding data indicate that the A_1 receptor is not particularly abundant in normal human lung, but its presence, possibly associated with nerves, is supported by functional studies. Adenosine A_1 receptors are present on human neutrophils, activation of which promotes chemotaxis [62] and increased adherence to endothelial cells [63, 64]. With specific regard to asthma, it has been shown that rabbits immunised at birth with antigen develop airways hyperreactivity to adenosine by a mechanism involving upregulation of the A_1 receptor [65, 66]. In an elegant extension of these studies, combined pharmacological and antisense approaches confirmed that adenosine-receptor mediated bronchoconstriction in the rabbit is mediated by the A_1 receptor [67]. Using antisense oligodeoxynucleotides targeted against the A_1 receptors of the lung to reduce their numbers, they were also able to show that sensitised animals without the A_1 receptor manifested a reduced bronchoconstrictor response to allergen challenge [67]. In a recent study of mice lungs, all four of the adenosine receptors have been detected, with A_1-receptor transcripts being the most abundant [6]. These authors also found a significant increase in transcript levels of the A_1, A_{2A} and A_{2B} receptors in the lungs of adenosine-deaminase deficient mice, which was seen in association with lung inflammation and increased airways hyperresponsiveness. Although these data lend some support to the evidence of adenosine A_1 receptor as a potential therapeutic target for allergic asthma or COPD, at the present time, there is no confirmation that this receptor subtype is involved in airway responses to adenosine in humans.

Adenosine A_{2A} receptors

Both A_{2A} and A_{2B} receptors have been identified by reverse-transcriptase polymerase chain reaction (RT-PCR) and in human bronchoalveolar lavage mast cells [57, 68]. The subunit s of G-protein (Gs)-coupled adenosine A_{2A} and A_{2B} receptors are distinguished by their high and low affinity, respectively, for adenosine [2]. The A_{2A} receptors most relevant to human lung disease are those expressed on mast cells [57, 68], neutrophils [69] and T-cells [70]. In contrast to A_{2B} receptors, A_{2A} activation results in suppression of histamine and tryptase release from human mast cells [68, 71, 72]. This could provide a balanced control mechanism. It is possible that at low concentrations of adenosine, only the off-signal provided by engagement of the higher affinity A_{2A} receptors prevails, thus

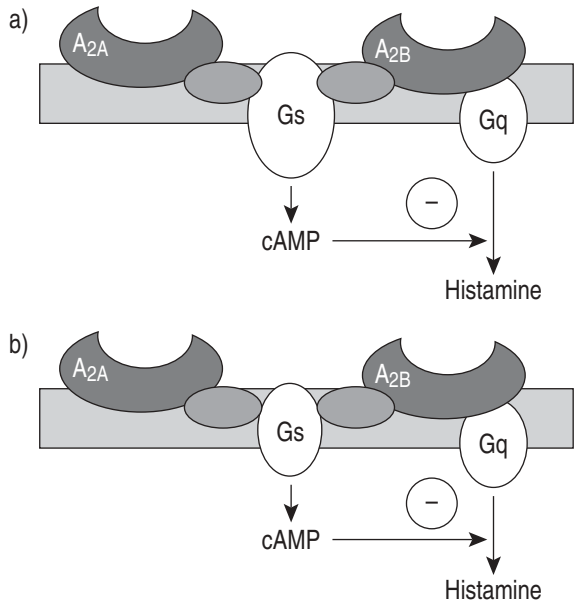

Fig. 3.– Diagram hypothesising the mechanism by which adenosine enhances histamine release from human airway mast cells in asthma. a) Normally, stimulation of the high-affinity A_{2A} adenosine receptor by adenosine leads to the generation of large quantities of intracellular cyclic adenosine 5′-monophosphate (cAMP), which downregulates the biochemical pathways implicated in the release of histamine. b) Possible scenario in asthma, where in the presence of high concentrations of adenosine the relative importance of the low-affinity A_{2B} receptor becomes greater with prevalent activation of regulatory subunit q of G-protein coupled receptor (Gq) proteins with significant mast-cell degranulation. In addition, downregulation of the subunit s of G-protein coupled receptor (Gs) function leads to a reduction of cAMP generation with subsequent reduced negative modulation on histamine release.

downregulating mast-cell mediator release (fig. 3a). Conversely, in situations in which high concentrations of adenosine are reached, such as in asthma and COPD [4], the relative importance of the low-affinity A_{2B} receptor becomes greater with significant mast-cell degranulation (fig. 3b). In addition to its putative role on human lung mast cells, adenosine appears to exert important effects on neutrophils. It is well known that stimulation of A_{2A} receptors abates neutrophil adherence to the endothelium [63], prevents upregulation of integrin expression on formyl-Met-Leu-Phe-stimulated neutrophils [73] and inhibits degranulation of activated neutrophils and monocytes [74–76]. Therefore, administration of an A_{2A} receptor agonist might exhibit anti-inflammatory potential in a disease such as COPD, where neutrophil-/monocyte-mediated tissue injury is strongly implicated. Unfortunately, A_{2A} receptors have a broad anatomical distribution (table 1) and they are important in mediating a number of responses in other body structures and cell systems, including inhibition of platelet aggregation, vasodilatation and a variety of effects on the central nervous system [78]. A selective topical action in the lung would be necessary to avoid unacceptable side-effects. Conversely, specific antagonists at A_{2A} receptors may enhance neutrophil activation and aggravate inflammation.

Adenosine A_{2B} receptors

Recently, the application of molecular cloning techniques identified the human adenosine A_{2B} receptor [54]. The A_{2B} receptor is structurally closely related to the A_{2A} receptor, and like the A_{2A} receptor, could raise intracellular cAMP when activated. Functionally, however, it appears to be very different from the A_{2A} receptor, which suggests that signal-transducing systems other than those directly linked to adenyl cyclase might be more important for its function [79]. The adenosine A_{2B} receptor has recently been identified immunochemically in human bronchial epithelium [80] and functional A_{2B} receptors have been found in endothelial cells, muscle cells, neurons, glial cells, neurosecretory cells, fibroblasts, and mast cells [57, 81]. Activation of A_{2B} receptors in the human mast cell line HMC-1 augments IL-8 release *per se* and potentiates phorbol 12-myristate 13-acetate (PMA)-induced secretion of IL-8 [58]. HMC-1 cells co-express A_{2A} and A_{2B} receptors, both of which are coupled with adenylate cyclase through G-proteins, but only A_{2B} receptors activate HMC-1 cells to release IL-8. Thus, adenosine would contribute to the pathogenesis of inflammatory airways disease by

Table 1.– Pharmacological classification and anatomical distribution of adenosine-receptor subtypes

Receptor subtype	Agonists[#]	Antagonists[#]	Distribution
A_1	CHA>NECA>>CGS21680	DPCPX>XAC>CGS15943>SPT	Heart, adipocytes, respiratory smooth muscle, neutrophils, kidney, hippocampus, cortex
A_{2A}	CGS21680 ≈ NECA>> CHA	ZM241385 ≈ SCH58261 ≈ CGS15943 ⩾ XAC>DPCPX	Platelets, neutrophils, vasculature, pancreas, mast cells, striatum
A_{2B}	NECA>CHA>> CGS21680	XAC>CGS15943>DPCPX	Vascular, intestinal and respiratory smooth muscle, chromaffin tissue, mast cells, brain
A_3	2-C1-IB-MECA>APNEA> NECA ≈ CGS21680	MRS1220 ≈ IABOPX> L268605>>XAC>DPCPX	Testis, kidney, lung, mast cells, eosinophils, neutrophils, heart, cortex, striatum

[#]: Full details on the adenosine receptor agonists and antagonists and the abbreviations can be found in [77]. >: greater than; >>: much greater than; ≈: approximately equal to.

acting on the mast cell A_{2B} receptor to enhance the release of proinflammatory mediators [2]. Given that inhaled adenosine only elicits bronchoconstriction in subjects with asthma and COPD [7, 8] and has no effect on the airway calibre of normal individuals, there appears to be an intrinsic difference in the way adenosine interacts with mast cells from patients. Although the response produced *in vitro* by A_{2B} receptors in HMC-1 cells appears to mimic the *in vivo* responses to inhaled adenosine in asthma and COPD, the molecular mechanisms behind the differential responses in asthma/COPD patients compared with normal controls remain to be elucidated. Several mechanisms could explain these discrepancies, including differential coupling of A_{2B} receptors to intracellular pathways and diversity at the receptor level, such as that based on different levels of affinity for A_{2A} and A_{2B} receptors (fig. 3). Although adenosine appears to mediate its effects mainly through adenosine-receptor activation in inflammatory cells, combined functional and radioligand binding studies have demonstrated that human airway smooth muscle is also a direct target of adenosine, with effects determined by differential contributions of time-dependent A_{2B} and A_1 adenosine receptors [82]. Accordingly, the relative distribution and activation of adenosine-receptor subtypes in airway smooth muscle may influence airway function in diseases such as asthma and COPD and warrant consideration in therapeutic strategies that target adenosine receptors or alter nucleotide/nucleoside levels in the airway.

The argument for A_{2B}-receptor activation being integral to the pathophysiology of asthma and COPD receives further support from consideration of the pharmacological properties of theophylline. Theophylline has affinity for human A_{2B} receptors at therapeutic blood concentrations but is not selective since it shows similar or lower affinities for both the A_1 and A_{2A} receptors. Given the limited role of the adenosine A_1 and A_{2A} receptors outlined above and the fact that therapeutic doses of theophylline have been shown to produce a greater inhibition against the bronchoconstrictor response to adenosine than against histamine [83], blockade of the A_{2B} receptor seems a plausible explanation for the clinical benefit seen with the drug. Moreover, the methylxanthine phosphodiesterase inhibitor, enprofylline, which has a similar anti-asthmatic activity to theophylline [84], has been recently shown to serve as a selective A_{2B}-receptor antagonist at therapeutic blood levels [58]. Selective antagonists of the A_{2B} receptor may provide a more potent and safer alternative to theophylline and enprofylline.

Adenosine A_3 receptors

Both *in vitro* [17, 85] and *in vivo* [86, 87] studies have established that activation of A_3 receptors results in mast-cell degranulation and/or enhancement of mast degranulation in response to allergen in a variety of rodent species. However, A_3-receptor protein was not found in association with human lung mast cells [18], thus questioning its relevance in the mechanism of adenosine-induced bronchoconstriction in humans. There is now accumulating evidence that A_3-receptor activation modulates functional changes in a variety of human immuno-inflammatory cells. For example, in the human lung, A_3 receptors are expressed on eosinophils in a relatively high density [88] and mediate inhibition of eosinophil chemotaxis when activated [18, 89]. In addition, these authors demonstrated that expression of the A_3 receptor (messenger ribonucleic acid (mRNA) and protein) was enhanced in the asthmatic lung [18]. Recently, EZEAMUZIE and PHILIPS [90] have shown that these receptors mediate two important anti-inflammatory functions of human eosinophils: the inhibition of the degranulation and suppression of oxygen radical generation. Adenosine A_3-receptor activation has also been implicated in: the suppression of tumour necrosis factor (TNF)-α release from human monocytes by endotoxin [91]; the inhibition of neutrophil degranulation induced by endotoxin or TNF-α in whole human blood [76]; and the modulation of T-cell function [92]. These findings have subsequently raised the question of the functional roles of these receptors. It is possible that the high adenosine concentrations found in the lungs of patients with asthma and COPD may be sufficient to produce significant inhibition. In this case, the presence of high levels of adenosine may represent a way for attenuating eosinophilic and neutrophilic inflammation *via* A_3-receptor activation. Thus, selective A_3 agonists may be valuable as anti-inflammatory drugs with a useful potential in the treatment of conditions such as asthma and COPD, where activated eosinophils and neutrophils play an important role.

Conclusions

Recognition of the potential role of adenosine receptors in the pathogenesis of chronic airway inflammatory diseases raises the possibility that blockade of these receptors may be a valuable approach to the treatment of asthma and chronic obstructive pulmonary disease. Promising adenosine receptor targets for novel therapeutics of asthma and chronic obstructive pulmonary disease have been recently identified in a number of inflammatory cell types, including mast cells, eosinophils, lymphocytes, neutrophils, and macrophages. However, the human lung mast cell appears to be the most attractive cellular target because of the unique modulation of its pharmacological characteristics and functional effects in response to inflammatory stimuli. Mast cells are likely to play a major role in the bronchoconstrictor response to inhaled adenosine both in asthma and in the active inflammatory phase of chronic obstructive pulmonary disease. Stimulation of A_{2B} receptors expressed on the surface of the human lung mast cell is likely to be the main trigger for adenosine-induced bronchospasm. Therefore, development of potent and selective A_{2B} adenosine-receptor antagonists for use in humans appears particularly beneficial and may further increase knowledge of the role of these receptors in physiological and pathological conditions.

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