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Review

Adenosine receptors and vascular inflammation ☆

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ABSTRACT

Epidemiological studies have shown a positive correlation between poor lung function and respiratory disorders like asthma and the development of adverse cardiovascular events. Increased adenosine (AD) levels are associated with lung inflammation which could lead to altered vascular responses and systemic inflammation. There is relatively little known about the cardiovascular effects of adenosine in a model of allergy. We have shown that A_1 adenosine receptors (AR) are involved in altered vascular responses and vascular inflammation in allergic mice. Allergic A_1wild-type mice showed altered vascular reactivity, increased airway responsiveness and systemic inflammation. Our data suggests that A_1 AR is pro-inflammatory systemically in this model of asthma. There are also reports of the A_{2B} receptor having anti-inflammatory effects in vascular stress; however its role in allergy with respect to vascular effects hasn't been fully explored. In this review, we have focused on the role of adenosine receptors in allergic asthma and the cardiovascular system and possible mechanism(s) of action. This article is part of a Special Issue entitled: "Adenosine Receptors".

Contents

1. Generation of adenosine and its metabolism

Adenosine is a ubiquitous purine nucleoside with multiple physiological effects. It has several regulatory functions including relaxation of the vascular smooth muscle, neuromodulation, regulation of inotropy and chronotropy, amongst others [1]. Under normal physiological conditions, adenosine is formed by the intracellular conversion of S-adenosyl-L-methionine (SAM) to S-adenosyl-L-homocysteine (SAH), which is then converted to adenosine and homocysteine by SAH-hydrolase [2,3]. Adenosine can also be produced extra-cellularly through successive dephosphorylation of ATP; ATP is dephosphorylated to ADP and then AMP which is converted to adenosine via ecto-5′-nucleotidases [4,5]. Adenosine, thus produced, can be further converted to inosine by the enzyme adenosine deaminase (ADA) and finally is broken down to uric acid

Abbreviations: AC, Adenylyl cyclase; ACh, Acetylcholine; ADA, Adenosine deaminase; AD, Adenosine; ADP, Adenosine diphosphate; AR, Adenosine receptor; AK, Adenosine kinase; AMP, Adenosine monophosphate; BAL, Bronchoalveolar lavage; cAMP, Cyclic adenosine monophosphate; CCPA, 2-chloro-N6-cyclopentyladenosine; CGS 21860, 2-*p*-(2-carboxyethyl)phenethylamino-5′ N-ethylcarboxy amidoadenosine hydrochloride; COPD, Chronic obstructive pulmonary disease; CV, Cardiovascular; CVD, Cardiovascular disease; DAG, Diacylglycerol; DPCPX, 1,3-Dipropyl-8-cyclopentylxanthine; IP_3, Inositol triphosphate; LO, Lipoxygenase; LT, Leukotriene; KO, Knockout; NECA, N-ethylcarboxamide-adenosine; SAH, S-Adenosyl-L-homocysteine; SAH-hydrolase, S-Adenosyl-L-homocysteine-hydrolase; SAM, S-Adenosyl-L-methionine; WT, Wild type

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which is excreted in urine. Adenosine can be phosphorylated to AMP via the enzyme adenosine kinase. Extra-cellular concentrations of adenosine are elevated several-fold during periods of increased metabolic demand, injury or stress such as ischemia [6] and inflammation.

2. Adenosine receptors

Adenosine acts on specific cell surface purinergic receptors to induce various physiological effects, and thus far, four subtypes have been identified, namely A_1, A_{2A}, A_{2B} and A_3. All four adenosine receptors are G-protein coupled and the effects that adenosine produces depends on both the receptor subtype that is activated as well as organ/tissue in which the receptor is present. A_1 and A_3 receptors are coupled to G_i while the A_{2A} and A_{2B} receptors are coupled to G_s. A_1 and A_{2A} have a high affinity for adenosine, while A_{2B} is low affinity and A_3 is intermediate [7,8]. The A_1 receptor signals through $G_{i/}G_o$-proteins and its activation leads to an inhibition of adenylyl cyclase (AC) which causes a lowering of cyclic AMP (cAMP). Signaling through the A_1 receptor can also lead to the activation of IP_3/DAG through the PLCβ-III pathway [9]. The A_{2A} receptor signals through the G_s pathway and its activation leads to stimulation of AC resulting in increased production of cAMP. The A_{2A} receptor is mainly anti-inflammatory and is involved in coronary vasodilation as well as vascular smooth muscle relaxation to various degrees depending on the species [10–12]. The A_{2B} receptor signals through $G_{s/q}$ and its activation can either result in increased cAMP or IP_3/DAG and Ca^{2+} levels. Lastly, the A_3 receptor signals through G_i and is negatively coupled to AC [13].

3. Asthma

Asthma is a chronic lung disease characterized by inflammation and airway hyper-reactivity. There are over 16 million people diagnosed with asthma in the US, with 7 million under the age of 18 years. Allergic asthma accounts for about half of these numbers. The disease consists of episodic events which manifest as hyper-responsiveness of the airways to common triggers like dust, pollen, cold air, exercise, cigarette smoke and other pollutants, resulting in bronchospasm and difficulty in breathing. Airway obstruction occurs due to inflammation, excessive mucus production, and overactive bronchial smooth muscle. Initially, the inflammation is acute in nature but eventually becomes chronic with the progression of the disease, and long term effects of asthma are linked to its inflammatory component. Disease management consists of anti-inflammatory drugs, leukotriene modifiers and bronchodilators.

4. Adenosine and asthma

Adenosine has long been implicated in the pathogenesis of asthma [14]. Inhalation of adenosine was shown to be a potent bronchoprovocant in asthmatic patients [15]. Inosine, the deaminated metabolite of adenosine does not produce bronchoconstriction [16] suggesting that the effect on bronchial smooth muscle is specific to adenosine and possibly involves adenosine receptors. Increases in adenosine levels correspond to increased airway inflammation and tissue damage, and asthmatic patients also have significantly higher levels of adenosine in bronchoalveolar lavage fluid (BAL) and exhaled breath condensate than normal healthy subjects [17,18]. Adenosine causes degranulation of mast cells which leads to the release of histamine and subsequent cascade of events including H_1 receptor-mediated bronchoconstriction and inflammatory response [19,20]. This mast-cell mediated response is believed to occur through the A_{2B} receptor although this has not been conclusively proven as yet [21].

Mice that lack the adenosine deaminase (ADA) enzyme have large amounts of adenosine in their lungs and severe lung inflammation [22]. In fact, these mice are unable to survive beyond three weeks due to respiratory distress. ADA deficient mice demonstrate the presence of eosinophilia in the lungs, extensive mast cell degranulation and increased levels of serum IgE [23], indicating a strong correlation between chronic elevation of adenosine levels and increased lung inflammation. There is evidence that adenosine causes recruitment of inflammatory cells to the lung [24] and amplification of the inflammatory response [25].

In allergic mice, adenosine, among other inflammatory mediators from allergic lung and activated leukocytes, is released [16,26]. This adenosine may be involved in further release of chemotactic and inflammatory mediators in the lung and systemic circulation by acting on its receptors present on different cells including mast cells, eosinophils, neutrophils and other inflammatory cells [25,27–29]. Experimentally induced temporary elevations in lung adenosine levels through the inhalation of adenosine (resulting from breakdown of adenosine 5′-monophosphate) have been shown to cause an increase in infiltration of eosinophils in patients with asthma [30].

5. Reactive airway diseases and cardiovascular complications

There is epidemiological evidence indicating that people suffering from asthma, chronic obstructive pulmonary disease (COPD) and reactive airway diseases are at an increased risk for developing cardiovascular disease (CVD) [31–33]. There is an association between atherosclerosis and stroke with reactive airway diseases. One study found that adult-onset asthma was associated with increased carotid atherosclerosis in women [34]. Impaired lung function has been found to be a risk factor for CVD [35]. Bronchial hyper-responsiveness to methacholine is associated with increased carotid intima-media thickness [36]. One of the leading causes for hospitalizations and deaths occurring in COPD patients is cardiovascular events [37].

Recent evidence in animal models indicates that CV complications associated with asthma are independent of asthma therapy and could be a result of asthma itself. Myocardial ischemia–reperfusion injury was enhanced in a rabbit model of systemic allergy and asthma [38] and allergic inflammation in the airways enhanced neutrophil recruitment to the myocardium and severity of ischemia–reperfusion in a murine model [39]. Allergic mice have poor vascular responses and systemic inflammation, with adenosine aerosol exacerbating these effects [40]; Table 1). In our study, we found that use of an A_1 AR antagonist ameliorated some of these effects, which led to the hypothesis that A_1 receptor is involved in pro-inflammatory effects systemically in a mouse model of allergic asthma.

6. Adenosine receptors in asthma and vasculature

Adenosine has a well established role in the control of vascular tone, and its effects are exerted through the activation of four ARs [41]. A_1 and A_3 ARs have been shown to be involved in vasoconstriction [9,42–44] whereas A_{2A} and A_{2B} ARs cause vasorelaxation [45–47].

The four ARs have different modulatory roles in asthma, and the cardiovascular system [48–50]. Many reports suggest that the A_1 AR is involved in direct bronchoconstrictor effects of adenosine. The

Table 1
Vascular responses to adenosine in Balb/C mice aorta [40].

Group	Response to 10^{-4} M adenosine (%)
Control	21.44 ± 3.94
Allergic	7.02 ± 2.94 *
Allergic + adenosine	-4.45 ± 3.8 (contraction) * #

+ Relaxation; − contraction.
* $P<0.05$ compared to control.
\# $P<0.05$ compared to allergic tissues.

expression of A_1 AR was found to be elevated in a rabbit model of asthma and the use of an A_1 antisense nucleotide to inhibit this upregulation resulted in blunted bronchoconstriction to adenosine [51,52]. Use of a selective A_1 antagonist (L-97) produced significant reduction of airway hyper-responsiveness in allergic rabbits by blocking these receptors [53]. A recent study reported that the expression of A_1 AR is significantly elevated in airway smooth muscle in asthmatic patients [54]. Other than the effects on airway smooth muscle, the A_1 AR has been implicated in increased mucin production in human tracheal cells [55] and in mediating monocyte phagocytosis [56]. All these studies suggest a strong role for the A_1 AR in asthma, both in airway obstruction and inflammation.

A_1 ARs also have systemic effects and are involved in blood pressure regulation [57] and vasoconstriction [9,42–44]. Recent studies suggest a role for A_1 AR in altered peripheral vascular reactivity and increased systemic inflammation [40]; Table 1 and Figs. 1, 2). In this study, Balb/C (A_1 wild-type: A_1WT) mice were divided into 3 groups: control or non-allergic (A_1WT CON), ragweed sensitized mice (A_1WT SEN) and ragweed sensitized mice further challenged with a single aerosol of adenosine (A_1WT SEN + AD) were studied.

The A_{2B} AR has been found to play a protective role in vasculature against arterial injury (vascular stress) and is involved in the regulation of TNF-alpha, which contributes to the anti-inflammatory actions of adenosine [58]. In A_{2B} receptor-null mice, the expression of vascular adhesion molecules was increased, as also the levels of pro-inflammatory cytokines [59,60]. A_{2B} antagonism also produced further impairment of adenosine-mediated aortic vasorelaxation in allergic mice [40].

Despite these data, there is little information specifically regarding the role of lung inflammation (as seen in asthma) in the development of cardiovascular disease, in relation to the vascular and systemic effects of adenosine. Systemic inflammation, endothelial dysfunction and altered vascular reactivity appear to be associated with asthma. Adenosine plays an important role in these effects and exogenously administered adenosine to increase the lung levels experimentally beyond the allergen exposure exacerbates observed outcomes.

Recent work from our lab [61] using A_1 AR knockout (A_1AR KO) mice has shown the involvement of A_1 ARs in systemic and vascular inflammation. Data showed that the allergic A_1WT mice (A_1WT SEN and A_1WT SEN + AD groups) had lower adenosine-mediated aortic relaxation to 5′-N-ethylcarboxamidoadenosine (NECA; non-selective adenosine analog) (Table 2) and higher contraction to 2-chloro-N6-cyclopentyladenosine (CCPA; selective A_1 AR agonist), with increased protein expression of A_1 AR in the aorta. There were also significantly higher levels of inflammatory markers in the plasma, and in aortic tissue. In contrast, no impairment in adenosine-mediated vascular responses was observed in A_1 AR KO (Table 2; allergic and non-allergic controls: control or non-allergic A_1KO CON, ragweed sensitized A_1KO SEN and ragweed sensitized further challenged with a single aerosol of adenosine A_1KO SEN + AD) aortic tissues. There were also significantly lower (or undetectable) levels of inflammatory markers in aortic tissue in allergic KO mice. These data implicate the A_1 AR in the deleterious systemic effects in allergic mice that may occur as a result of inflammation. The exact signaling mechanism(s) of the A_1 AR remains to be elucidated.

The A_{2A} receptor has been reported to have anti-inflammatory and protective role in the lung, especially lung injury A_{2A} KO mice were shown to have higher levels of pro-inflammatory cytokines and extensive tissue damage when subjected to an inflammatory insult that were less in the corresponding A_{2A} WT mice [62].

Our lab has reported that A_{2A} KO mice have higher oxidative stress that leads to impaired tracheal relaxation [63]. There have also been reports that the A_{2A} AR protects against myocardial ischemia reperfusion injury [64]. In some preliminary data from our lab (unpublished), we have also observed that allergic A_{2A} KO mice have poor aortic relaxation and increased airway response (whole body

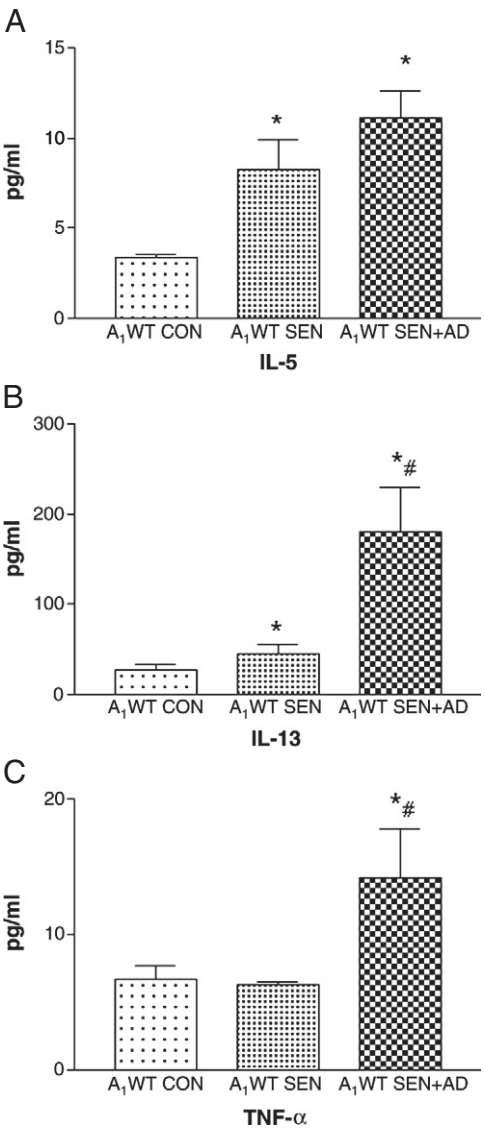

Fig. 1. Systemic inflammatory markers in plasma A) IL-5 B) IL-13 C) TNF-α in A_1WT non-allergic control (A_1WT CON), A_1WT allergic (A_1WT SEN), A_1WT allergic further challenged with adenosine (A_1WT SEN + AD) mice [40] *P<0.05 compared to WT CON; #P<0.05 compared to WT SEN.

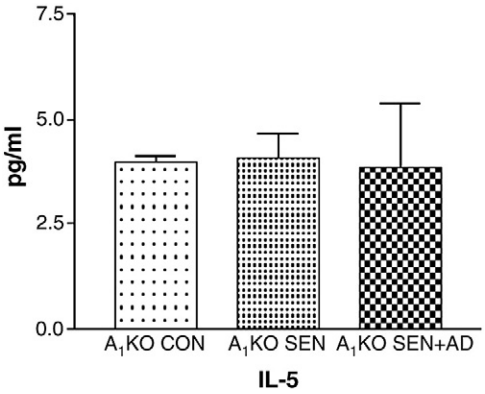

Fig. 2. Plasma levels of IL-5 in A_1KO non-allergic control (A_1KO CON), A_1KO allergic (A_1KO SEN), A_1KO allergic further challenged with adenosine (A_1KO SEN + AD) mice (unpublished observation; IL-13 and TNF-α were not detected in A_1KO plasma).

Table 2
Vascular responses to 5′-N-ethylcarboxamidoadenosine (NECA; non-selective AR agonist) in A_1 wild-type and knockout Balb/C mice aorta [61].

Group	Response to 10^{-5} M NECA (% relaxation)
A_1WT control	48.64 ± 2.98
A_1WT allergic	28.08 ± 5.06*
A_1WT allergic + adenosine	17.4 ± 5.53*
A_1KO control	43.0 ± 2.45
A_1KO allergic	48.48 ± 1.93
A_1KO allergic + adenosine	48.2 ± 1.47

* $P<0.05$ compared to WT control.

plethysmography) compared to WT. All these findings lead us to speculate that the A_{2A} AR may protect against vascular inflammation.

Reports have suggested that activation of A_3 receptor by inosine [65] as well as adenosine [66] leads to mast-cell induced increase in vascular permeability and extravasation. A_3 receptors can also have anti-inflammatory effects [67]. The A_3 AR also increases mucin production in asthma [68] and has been shown to be involved in bronchoconstriction and eosinophilia [69,70]. Other reports suggest an anti-inflammatory role for A_3 receptors in diseases like rheumatoid arthritis [71]. The role of the A_3 receptor thus could possibly be both pro- and ant-inflammatory. How this receptor behaves in the vasculature in allergic mice remains to be seen.

7. Possible pathway for adenosine-induced vascular changes in asthma

Based on the literature and some of our data, we hypothesize a speculative pathway for lung inflammation leading to systemic effects (Fig. 3). We found that IL-13 levels were highest in allergic mice [40]. A review of the literature shows a close relationship between IL-13 and adenosine in lung inflammation [72]. IL-13 is an important mediator in asthma and has been implicated in lung inflammation and airway remodeling. It is a product of mast cell degranulation and is also released from T-helper 2 (Th2) cells. Adenosine and IL-13 interact with each other positively as shown in studies done with asthmatic mice [72].These authors found that IL-13 caused a progressive increase in adenosine accumulation, inhibited the activity of adenosine deaminase, and augmented the expression of the A_1, A_{2B}, and A_3 ARs. Their findings suggest that adenosine signaling influences the severity of IL-13 and Th2-mediated disorders such as asthma.

IL-13 signaling occurs through the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway. This cytokine acts on its receptor (via JAK-1) and leads to phosphorylation

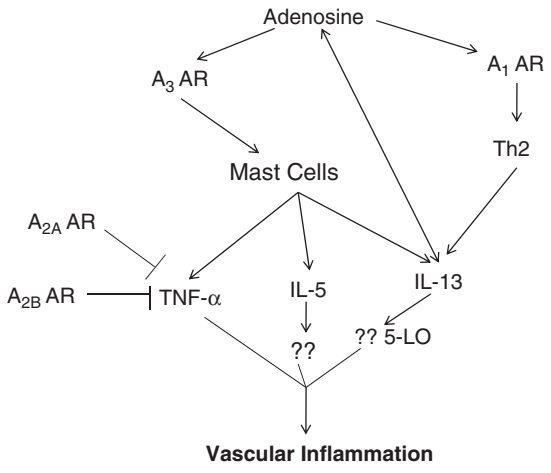

Fig. 3. Possible pathway for adenosine receptors as both pro- and anti-inflammatory effectors in vascular inflammation in asthma. "??" indicates unknown or possible mediators.

of STAT6, which induces the transcription of several genes including 5-lipoxygenase (5-LO). 5-LO, via the arachidonic acid pathway, produces inflammatory leukotrienes (LTs) which are very important mediators of IL-13 induced lung injury [73]. Recent studies have also suggested a pro-atherosclerotic role for LTs with LTB_4 acting as a potent leukocyte chemoattractant that amplifies inflammation in atherosclerosis [74].

IL-13 and IL-4 act synergistically with TNF-α to increase eotaxin levels in the lungs. Eotaxin increases lung eosinophilia in asthma and is very important in amplification of eosinophilic inflammation. Though eosinophilia is considered to be a characteristic hallmark of asthmatic inflammation, eosinophils are not found in any significant amounts in atherosclerotic lesions. Eotaxin may have a novel role in atherosclerosis independent of eosinophils. Haley et al. have reported that eotaxin and its receptor, CCR3, were overexpressed in the inflammatory infiltrate of human atheroma [75]. CCR3 was predominantly expressed on macrophages and they suggest eotaxin may participate in mast cell activation or recruitment. In addition to this, in our most recent study [61] we have found significantly higher levels of IL-5, a cytokine positively linked with eosinophilia, in aortic tissue of allergic A_1WT mice. This may further support a role for IL-5 induced eotaxin effects in vasculature.

In conclusion, adenosine-mediated effects in asthma may extend beyond the lung and have consequences both systemically and in the vasculature. It is possible that inflammation underlies these additional effects and there is evidence so far for the A_1 AR having a pro-inflammatory role. There remains much to be learnt in this field, with each adenosine receptor's role not yet delineated. Such studies would help to further the potential of adenosine agonists and antagonists as therapeutic agents for systemic and vascular inflammation from a number of disorders including hypertension, diabetes, rheumatoid arthritis and many other complications.

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