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Perspective

Adenosine signaling in airways: Toward a promising antiasthmatic approach

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ABSTRACT

Adenosine participates to asthma physiopathology by signaling through more than just one receptor subtype. Defining the role of each receptor is complicated by evidence that often results obtained on rodents do not coincide with human studies, but what emerges is that an important condition to establish hyperresponsiveness to adenosine in any species of sensitized animals is the exposure to allergen; this feature appears to be very similar to the human situation, since allergic humans regularly undergo exposure to allergen. Furthermore, A_{2B} in humans, but A_3 receptor in rodents, would mediate, indirectly, the bronchoconstriction in response to adenosine and would play the main role in adenosine-induced airway inflammation and airway hyperreactivity. On the other hand, A_1 receptor over-expressed on asthmatic airways would mediate a direct adenosine bronchoconstrictor effect. Antagonists and agonists to adenosine receptors have been considered as antiasthmatic drugs but often their development has been limited by unwanted effects. Preventing adenosine accumulation in airways should be considered as a novel promising antiasthmatic strategy.

1. Adenosine signaling in inflammation

Adenosine is a nucleoside always present both within and outside cells in nanomolar concentration (10–100 nM) under physiological conditions, deriving by the breakdown of adenine nucleotides. Physiologically, adenosine concentrations are constant and finely regulated by cellular re-uptake, conversion to inosine, phosphorylation to AMP. Conversely, following trauma or cellular stress, such as during hypoxia, ischemia or inflammation, its levels increase rapidly following ATP degradation, and may rise up to 100 μM (Fredholm, 2007).

Two ecto – enzymes, the nucleoside triphosphate diphosphohydrolases (NTPDase1; CD39) and ecto 5' nucleotidase (CD73) that are extracellular membrane bound enzymes are involved in the adenine nucleotides (ATP, ADP and AMP) breakdown and the following extracellular adenosine accumulation; their activity and/or cellular expression may vary following tissue injury (Longhi et al., 2013; Zimmermann, 2000).

Extracellular adenosine accumulation represents an early endogenous signal controlling inflammation and immune responses through the interaction with four cell surface G-protein coupled receptors, indicated as A_1, A_{2A}, A_{2B} and A_3. Although binding the same agonist, adenosine receptors differ in several aspects, including their expression profile in different cell types, under physiological or pathological conditions; the identity of the *G* – proteins to which they are coupled; their affinity for the agonist and their sensitivity to phosphorylation. All these factors combined determine the extent, the duration and the outcome of cellular exposure to adenosine and, in the end, dictate the nature of the response to adenosine tissue accumulation that may be beneficial or detrimental (Bours et al., 2006). A_1, A_{2A} and A_3 receptors have the highest affinity being activated by physiological adenosine concentrations (EC_{50} 0.01–1 μM), lower than those required for the lowest affinity receptor A_{2B} (EC_{50} 24 μM) that are likely reached only in a pathological environment. Nonetheless, besides receptor affinity, and thus adenosine concentration, response to adenosine depend also upon the relative expression of each receptor on a given tissue that may vary under pathological circumstances (Fredholm, 2010; Hua et al., 2011; Morello et al., 2006).

Evidence suggests that adenosine accumulation in an inflamed tissue might be a crucial signal able to activate and/or to sustain a chronic inflammation; in this respect, it would play a role in disease development since its ability to function as a paracrine mediator of the inflammatory response.

On the other hand, adenosine accumulation in an inflamed site has also been suggested to be part of endogenous immunosuppressive mechanisms acting to preserve host defense and tissue integrity; thus, in this respect it would play as a brake to limit tissue damage. However, it is now assumed that tissue adenosine

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accumulation may play a double role, beneficial or detrimental, depending on its concentrations in the milieu and on the persistence of its high concentrations; as well as on tissue physiopathological conditions and on receptor subtype activated (Bours et al., 2006). In airways, the concept of this double role of adenosine may be exemplified by taking into account two important experimental findings: one is that mice lacking CD39 or CD73, enzymes that are rate limiting for extracellular adenosine generation, are more susceptible to acute lung injury following mechanical ventilation (Eckle et al., 2007). On the other hand, mice deficient of adenosine deaminase (ADA), the enzyme that cause adenosine deamination to inosine, develop chronic pulmonary inflammation and airway obstruction (Blackburn et al., 2000). Thus, failure of the pathway leading to extracellular adenosine generation increases vulnerability to acute injury, while an excessive extracellular adenosine accumulation, such as in ADA deficient mice, causes chronic injury. Ultimately, moderate and short lasting increased levels of extracellular adenosine may function as a natural endogenous protective pathway, while strongly high and long lasting extracellular adenosine tissue levels may contribute to the extent of the inflammatory tissue damage (Haskó et al., 2008).

2. Adenosine and asthma

Bronchial asthma represents a chronic inflammatory disorder, characterized by airway hyperreactivity, inflammation and obstruction. Several inflammatory cells and mediators contribute to establish asthma symptoms and the progressive loss of airway functionality; however, the etiopathogenesis of the disease is unknown neither it has been established the type nor signaling molecules that govern the chronic nature of inflammation (Holgate, 2011).

There is much evidence that adenosine plays a role in bronchial asthma. First, Cushley et al. (1983) demonstrated that inhaled adenosine caused bronchoconstriction in asthmatics, allergic and non-allergic, but not in healthy subjects. Successively, it was shown that circulating adenosine levels increased in asthmatics following bronchoprovocation with allergen. Moreover, elevated levels of adenosine were also found in their bronchoalveolar lavage fluids (BALFs) (Driver et al., 1993; Mann et al., 1986).

Interestingly, in humans, bronchial sensitivity to adenosine has been shown to reflect allergic asthma and bronchial inflammation better than the sensitivity to other agents, such as methacholine. Such evidence has led to hypothesize that adenosine bronchoprovocation would be a diagnostically valuable test to differentiate asthma from other airway diseases, such as chronic obstructive pulmonary disease (COPD) (De Meer et al., 2002; Manso et al., 2011;Polosa and Holgate, 1997).

All adenosine receptor subtypes are expressed on human airways, either on stromal, resident or on recruited immune cells and all subtypes have been described to be involved in bronchial asthma; however, the contribute of each of them remains to be clarified (Wilson et al., 2009).

Clinical observations first suggested mast cell involvement in adenosine-induced bronchoconstriction, since following adenosine bronchoprovocation in humans, plasma histamine levels increased and the effect was abolished by both terfenadine and cromolyn sodium (Driver et al., 1991,1993; Phillips and Holgate, 1989; Phillips et al., 1989). However, adenosine was shown not to be able by itself to stimulate histamine release from mast cells but to increase histamine release from already "primed" mast cells (Hughes et al., 1984; Peachell et al., 1988). Such evidence well justify why only asthmatic subjects are responsive to adenosine, inasmuch as mast cells in asthmatic airways are phenotypically altered under the influence of Th2-cell derived cytokines and, likely, "primed" (Boyce, 2003).

Thus, bronchial response to adenosine in humans have initially been attributed to an indirect mechanism, involving mast cell activation, probably via A_{2B} receptor, and the release of mediators contributing either to acute or chronic symptoms of asthma (Feoktistov and Biaggioni, 1995; Forsythe and Ennis, 1999). On the contrary, A_3 and A_{2A} receptors on human cultured mast cells, isolated from umbilical cord blood, have shown to be protective, by inhibiting activation and mediator release (Suzuki et al., 1998). Recently, an in vitro study performed on primary human cultured mast cells (HCMC) isolated from adult peripheral blood that better resemble human tissue mast cells demonstrates that A_1 receptor increases histamine release from sensitized HCMC challenged with anti-IgE, while A_{2B} receptor plays an inhibitory role (Yip et al., 2011). The discrepancy among these studies may be attributed to an intrinsic difference in cultured mast cells obtained from different sources. Hua et al. (2011) have demonstrated that adenosine potentiates degranulation in response to anti-IgE of human umbilical cord blood mast cells previously incubated with IL-4 and Ig-E. The effect is paralleled by the increased expression of A_{2B} and the down-regulation of A_{2A} receptor. This finding outlines the importance of the inflammatory milieu to obtain mast cells sensitive to adenosine.

Different data have been obtained in experimental animals; indeed, in mice it has been shown that A_3 mediates mast cell activation (Tilley et al., 2003; Zhong et al., 2003), while A_{2B} and A_{2A} inhibit mast cell degranulation and cytokine production respectively (Hua et al., 2007, 2013).

In any respect, the indirect mechanism mast-cell mediated cannot account for the specific sensitivity to adenosine of human asthmatic airways observed either in vivo or in vitro (Bjorck et al., 1992; Cushley et al., 1983). Likely, adenosine signaling through A_{2B} receptor, which is widely distributed in airways, plays a major role in asthma development by promoting up-regulation of pro-inflammatory cytokines (Ryzhov et al., 2004; Zaynagetdinov et al., 2010; Zhou et al., 2009). This could be the mechanism by which increased levels of adenosine in asthmatic airways participate to establish the chronic nature of inflammation and airway hyperreactivity. On the other hand, an additional mechanism would be responsible for adenosine-induced bronchoconstriction in asthmatics.

The role of A_1 receptor was first investigated on an allergic rabbit model. It was found that only adult rabbits immunized from birth presented hyperresponsiveness to adenosine, suggesting the involvement of an inducible A_1 receptor due to immunization (Ali et al., 1994; el-Hashim et al., 1996). Successively, it was shown that, in the same model, an antisense oligonucleotide targeting A_1 receptor mRNA reduced bronchoconstriction induced by either adenosine or allergen (Nyce and Metzger, 1997). Consistent with results is the study performed by Smith and Broadley (2010) on guinea pigs demonstrating that A_1 receptor is involved in the late asthmatic response observed 24 h following allergen challenge; nonetheless, in this model, A_{2B} receptor has been demonstrated to be involved in the cell influx and the consequent airway hyperreactivity. We have recently demonstrated that sensitized Wistar rats develop A_1 receptor-mediated hyperresponsiveness to adenosine and to allergen 24 h following allergen challenge; the effect is paralleled by increased A_1 receptor expression on airways (Alfieri et al., 2012). Our study is consistent with the finding of A_1 overexpression on asthmatic bronchial tissues (Brown et al., 2008) and the hypothesis that exposure to allergen is critical to establish airway hyperreactivity and A_1 receptor up-regulation.

In other words, A_{2B} receptor would be involved in an early stage following allergen exposure and would mediate, as described above, adenosine induced inflammation and hyperreactivity. A_1 receptor

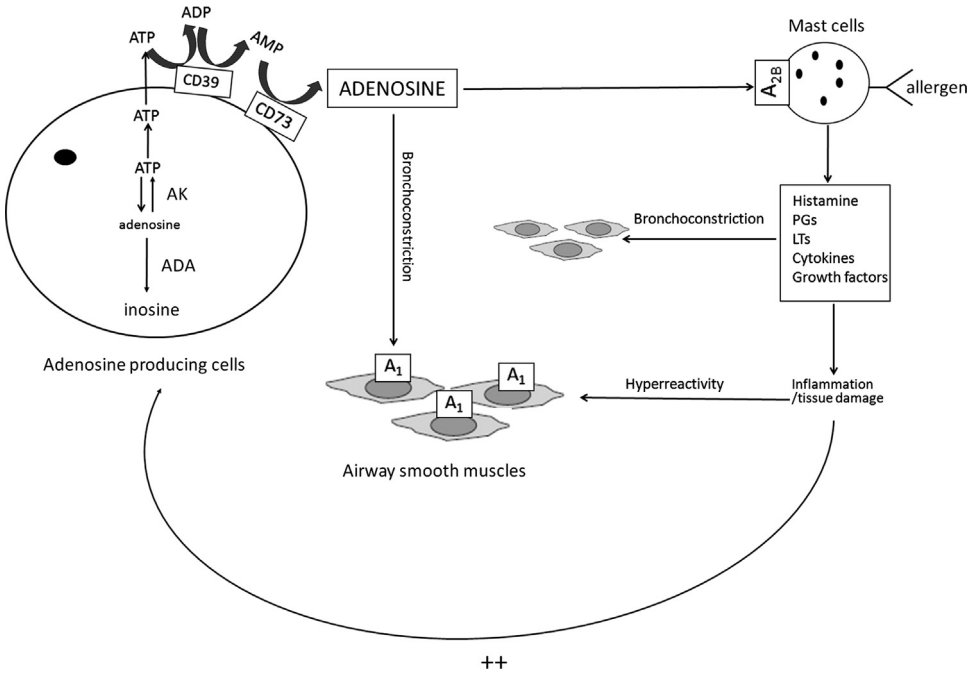

Fig. 1. Diagrammatic representation on the possible role of adenosine signaling in asthmatic airways. See text for details and further information. Abbreviations: AK, adenosine kinase; ADA, adenosine deaminase; PGs, prostaglandins; LTs, leukotrienes.

would be involved in a late stage following allergen exposure consistent with the requirement of its induction on airways and would mediate the direct bronchoconstrictor effect of adenosine (Fig. 1).

3. Conclusion and perspectives

When the study of the role of adenosine in bronchial asthma is approached, two important features must be considered: (1) its elevated levels found in BALFs of asthmatics and thus its ability to establish features of airway inflammation and the consequent bronchial hyperreactivity and (2) its ability to cause bronchoconstriction only in asthmatic airways. Mechanicistic basis underlying these two adenosine effects are likely distinct although overlapped under some aspects. What emerges is that A_{2B} in humans would mediate, indirectly, the bronchoconstriction in response to adenosine and would play the main role in adenosine-induced airway inflammation and hyperreactivity. Antagonists to this receptor would likely limit adenosine pro-inflammatory effects. In humans A_3 receptor has an anti-inflammatory role by inhibiting immune cell chemotaxis; such evidence has led to investigate on the antiasthmatic potential of A_3 agonists (Wilson et al., 2009).

A_1 receptor that in asthmatic airways is up-regulated by the chronic inflammation would be itself expression of an established airway hyperreactivity and would mediate hyperresponsiveness to adenosine and allergen (Alfieri et al., 2012; Bjorck et al., 1992; Brown et al., 2008); thus, it would be a good target for bronchodilator agents development. A_{2A} receptor, as widely demonstrated, mediates adenosine – antinflammatory effects (Wilson et al., 2009) thus agonists to this receptor would limit inflammation.

Adenosine receptors are practically expressed by all cell types and are involved in either physiological or pathological processes depending on both their relative cellular expression and adenosine concentrations in the milieu. Under these conditions, it is very difficult to achieve therapeutic concentrations with antagonists and/or agonists devoid of unwanted effects and thus to develop drugs targeting adenosine receptors as antiasthmatics.

A novel therapeutic approach would be to modulate endogenous adenosine production targeting CD39 and/or CD73, whose expression is regulated by cytokines in an inflammatory milieu (Longhi et al., 2013). The potential therapeutic of these enzymes has already been considered for several diseases (Forte et al., 2012; Schetinger et al., 2007) and, for airway diseases, it has been evaluated by studies performed on transgenic mice. CD73 – deficient sensitized mice do not develop airway hyperreactivity following allergen challenge, further confirming the important role for adenosine in setting the disease (Schreiber et al., 2008). Théâtre et al. (2012) have found that mice overexpressing CD39 present increased susceptibility to LPS-induced lung inflammation. Increased CD73 tissue expression has been found in lung of patients affected by COPD (Zhou et al., 2010). In the light of this knowledge CD39 and CD73 should be considered as promising targets for an antiasthmatic therapy aimed to switch off the disease rather than to block the symptoms.

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