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COMMENTARY

Finding better therapeutic targets for patients with asthma: adenosine receptors?

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Recent observations suggest a potential pathophysiological function for adenosine signalling in chronic inflammation of the airways, and development of new selective agonists or antagonists for adenosine receptor subtypes has recently lead to a number of clinical trials of such agents in asthma. The review by Wilson in this issue of the *BJP* provides a critical perspective on adenosine receptors as rational targets for drug development for anti-asthma drugs with a focus on their efficacy and safety. Important conclusions can be drawn about the function of adenosine receptors in human asthma and approaches to these important targets with novel therapeutic agents.
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Asthma is a common disorder estimated to affect 300 million people worldwide, with a prevalence of between 1 and 18% varying between countries and age groups (Bateman *et al*., 2008). It is a chronic inflammatory disorder of the airways characterized by some degree of mast cell and eosinophilic airway infiltration and activation, driven by specific cytokines and chemokines produced by CD4+ Th2 lymphocytes. The chronic inflammation is associated with progressive structural changes in the airway tissues and bronchial hyper-responsiveness that leads to the clinical manifestations of the disease: recurrent episodes of wheezing, breathlessness, chest tightness and coughing (Joos *et al*., 2003).

Although effective pharmacological treatment exists for asthma with anti-inflammatory and bronchodilator medication, many patients remain suboptimally controlled (Rabe *et al*., 2004), either due to the occurrence of severe refractory disease (Holgate and Polosa, 2006) or because of the high percentage of patients poorly compliant with inhaled treatments for asthma (Sherman *et al*., 2001). A few additional therapies are available and include methylxanthines, cholinoceptor antagonists, cromones and leukotriene modifiers, but these are of variable efficacy (Polosa and Morjaria, 2008). The introduction of a monoclonal antibody that is able to block IgE effects in severe allergic asthma is another breakthrough in asthma management but only for a limited number of patients (Polosa and Morjaria, 2008). Consequently, there is a compelling need for improved therapeutic strategies for patients with poorly controlled asthma, particularly for oral therapies that would enhance patient compliance.

In an effort to fill this gap, a host of pharmaceutical companies and research institutions are addressing the huge potential for the development of novel therapeutic agents that modulate adenosine signalling, with significant clinical advantage for chronic airway inflammation and asthma (Press *et al*., 2007).

The biological use of the nucleoside, adenosine, has evolved to modulate a wide array of physiological and immune responses in almost all mammalian tissues. In the context of asthma, high levels of adenosine appear to be associated with hypoxic and inflammatory conditions. Here, the primary action of adenosine is to reduce tissue injury and promote repair by different receptor-mediated mechanisms including the increase in oxygen supply/demand ratio, preconditioning, anti-inflammatory effects and stimulation of angiogenesis (Linden, 2005). Yet despite the beneficial function of adenosine as an endogenous anti-inflammatory regulator, chronically increased levels of adenosine in the airways may elicit a pro-inflammatory type of response.

Adenosine has recently received much attention with regard to its involvement in the pathogenic mechanisms for the initiation and maintenance of a chronic inflammatory response of the airways in asthma. Most of the evidence has derived from work in mice with genetic deletion of adenosine deaminase and with overexpression of the cytokine, interleukin-13, indicating that elevated levels of adenosine evoke strong inflammatory responses in the lung

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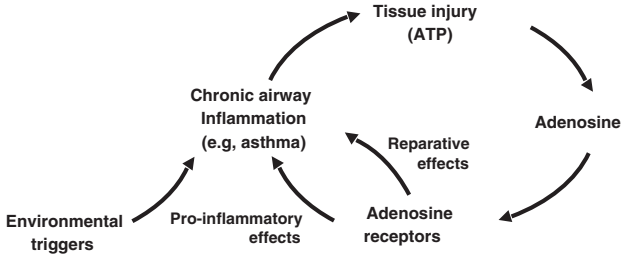

Figure 1 Proposed model for adenosine-mediated amplification pathway for chronic airway inflammation. Several different triggers and cellular mediators lead to the development of asthma. The resulting inflammation and tissue damage in the lung can create a hypoxic environment conducive to the formation of extracellular adenosine. Although normal levels of extracellular adenosine might serve important roles 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 subtypes of adenosine receptors.

with associated features of airway remodelling, tissue fibrosis and emphysema-like lesions (Blackburn *et al.*, 2003). Thus, when adenosine is generated in large amounts, as during inflammation, it can upregulate the expression of molecules that in turn enhance and sustain progression of inflammation, providing a compelling mechanism for adenosine-mediated amplification pathway for chronic airway inflammation and remodelling of the airways (Figure 1). However, the phenotype described in the adenosine deaminase-deficient mice is far from being typical of human asthma, there is no allergen and these mice are immune deficient (clearly two things not seen in human asthma) and one must be always cautious when interpreting results from any genetically modified mouse.

Further evidence linking adenosine signalling to chronic inflammatory airway disease is provided by cultured cell systems (see Caruso *et al.*, 2007). Several inflammatory and resident cell types known to have an important function in the pathogenesis, progression and exacerbation of chronic inflammatory airway diseases, constitutively express adenosine receptors and their activation through stimulation of these receptors leads to effects associated with the asthmatic phenotype. Although in cellular experimental *in vitro* systems, adenosine exerts predominantly anti-inflammatory and protective effects in response to tissue injury, through activation of high-affinity adenosine receptors, in the presence of elevated levels of adenosine (such as in the course of exacerbation of lung inflammation) it is possible that there is also activation and overexpression of low-affinity adenosine receptors. There are as many studies showing anti-inflammatory properties as pro-inflammatory properties of adenosine and this is probably dependent on the cell types and cytokine milieu in which the inflammatory end points are being examined. Adenosine receptors may be upregulated by inflammatory cytokines of great relevance to asthma pathogenesis, including tumour necrosis factor-α (Fortin *et al.*, 2006). However, the contribution of adenosine to the initiation and persistence of this inflammatory response appears to be quite unpredictable depending on the pattern of expression, function and affinity of the four known adenosine receptor subtypes and, unfortunately, there is no ideal *in vitro* model for the asthmatic human mast cell. Moreover, prediction of the inflammatory responses to adenosine signalling may be further complicated by the timing in the cell experiments, with adenosine receptors serving anti-inflammatory properties in acute phases of Th1-dominated models or disorders, whereas the same receptors serve pro-inflammatory features later on in the disease progression of the model. It would be a dangerous oversimplification to promote any one adenosine receptor as having only one biological or pathological function.

Yet the rationale for investigating the function of adenosine signalling in human asthma is strong (Caruso *et al.*, 2007). (1) For instance, levels of adenosine are elevated in the plasma, bronchoalveolar lavage fluid and exhaled breath condensate of patients with asthma. Also, exposure to adenosine aerosols induces a dose-related bronchoconstriction in patients with asthma but not in normal controls. Finally, therapeutic concentrations of non-selective, methylxanthine, adenosine receptor antagonists (theophylline, enprophylline and bamiphylline) have been shown to improve lung function and symptoms in subjects with asthma. Taken together, these observations suggest a potential pathophysiological function for adenosine signalling in asthma. Development of new selective agonists or antagonists for adenosine receptor subtypes has recently lead to a number of clinical trials in asthmatic subjects, which should clarify the risks and benefits of this therapeutic approach.

Looking into the future, the review article by Constance Wilson in this issue of the *BJP* (Wilson, 2008) gives an excellent overview of adenosine as an important signalling molecule in human asthma and provides a critical perspective on adenosine receptors as rational targets for drug development for anti-asthma drugs with an interesting emphasis on the A1 adenosine receptor. And perhaps this is a good thing, given that the function of the A1 adenosine receptor subtype as an important therapeutic target in human asthma has been often neglected. For instance, the notion that bamiphylline—a methylxanthine that has been in clinical use as an anti-asthma drug for over 20 years in Europe—produces its anti-asthma effects by specifically blocking A1 adenosine receptors, it is rarely reported and appears to support the view that A1 adenosine receptors may be a significant target. Furthermore, an upregulation of the A1 adenosine receptor subtype has been recently demonstrated by immunohistochemistry in bronchial biopsies of patients with asthma (Brown *et al.*, 2008).

Unfortunately, a close scrutiny of the current evidence reported in clinical trials fails to provide a convincing role for these agents. After reviewing all the publications about specific modulators of adenosine receptor signalling that have been or are currently being tested in humans, it is cogent to note that treatment of asthma with these compounds is of limited clinical efficacy. Consequently, despite a considerable increase in our understanding of the pathogenetic role of adenosine in chronic airway inflammation, it is surprising that this knowledge has not yet been translated into effective treatments for asthma. One possible reason for this is our lack of understanding 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. Perhaps, it is possible that combination of selective antagonist/agonists for different adenosine receptor subtypes will be required to obtain reasonable clinical efficacy. Alternatively, the local concentrations of the ligand (adenosine) under pathological conditions are likely to be of paramount importance in dictating the overall biological response and dissecting the factors involved in controlling these concentrations (for example, extracellular nucleotidases) is likely to be of greater significance. Given that the enhanced inflammation and damage seen in asthma leads to the observed increase in adenosine, it would be perhaps more efficient to reduce the overall level of adenosine signalling by suppressing airway inflammation with inhaled corticosteroids.

The pharmacological arsenal for allergy and asthma is fast growing (Holgate and Polosa, 2008) and significant endeavours in medicinal chemistry and pharmacology have yielded a substantial number of safer and highly selective compounds directed against the four known adenosine receptor subtypes. Some of them have already entered clinical development and may be of assistance in the process of finding better therapies for our patients with asthma. However, we will not have a definitive answer until larger and better designed proof-of-concept clinical trials in asthmatic patients are carried out.

Conflict of Interest

RP has participated as a speaker for CV Therapeutics, Novartis, Merck and Roche. He is also a consultant for CV Therapeutics, Duska Therapeutics and NeuroSearch.

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