Adenosine: a key effector molecule of asthma or just another mediator?

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ADENOSINE IS A PURINE NUCLEOSIDE with wide ranging intracellular functions linked to intermediary and nucleic acid metabolism. It is released from cells when under oxidative or metabolic stress and has a range of extracellular functions mediated through purinoceptors A1, A2A, A2B, and A3. In 1983, we first showed that inhaled adenosine, but notably not inosine (the adenosine deaminase metabolite) or guanosine, was a powerful bronchoconstrictor in asthmatic but not normal subjects (6). An almost identical response was also observed with inhaled adenosine, a 5'-monophosphate that is rapidly converted to adenosine by the ubiquitous ectoenzyme 5'-nucleotidase (16). Despite this evidence, the action of adenosine on airway smooth muscle in vitro has been conflicting, varying between species and, in the same species, with the type of preparation, the initial level of tone, and the concentration of adenosine used. In isolated human airway preparations, the predominant effect of the nucleoside is contraction, although its effect is weak (11). Airway preparations from allergic asthmatic subjects were more sensitive to the contractile responses of adenosine and related analogs, but the response could be almost entirely abolished by inhibition of contractile cysteinyl leukotriene, histamine H1, and prostanoïd effects (3). Together with cumulative evidence showing that adenosine-induced bronchoconstriction in asthma could be effectively blocked by inhibition of mast cell mediator release (23), antagonism of cysteinyl LT1 and H1 receptors (20, 24), and evidence showing that following exposure to AMP, increased levels of mast cell mediators could be detected in asthmatic airways (22), this provided the essential link to incriminate the mast cell as an effector of the acute asthmatic response to this nucleoside (21).

Studies on human lung mast cells established that adenosine could enhance IgE-dependent mediator release in vitro by interacting with cell surface purinoceptors of the A2 subtype (15, 18). Such a mechanism helped explain the preferential protective effect exerted by xanthines such as theophylline against adenosine-induced bronchoconstriction (7), which may be relevant to the therapeutic efficacy of this drug class in asthma (9). Subsequently, two subtypes of A2 receptor have been uncovered, A2A (linked to Gs coupling) and A2B (linked to Ga and Gq coupling), the latter being responsible for the augmenting properties of adenosine on human mast cells (8). In rats, this effect is also said to be served by the A2B receptor (13), whereas, in mice, the A3 receptor subsumes this function (17). The ability of adenosine released in inflamed airways to enhance mast cell mediator release via the A2B receptor has led to this receptor being identified as a novel therapeutic target in asthma. Enprofylline, which is a weak but selective A2B antagonist, has been shown to be highly effective in asthma (5), but, unfortunately, the further development of this drug had to be discontinued due to toxicity unrelated to its primary pharmacology.

The recent discovery by Blackburn and colleagues (4) that adenosine deaminase-deficient mice exhibit a lung phenotype with features of asthma including bronchial hyperresponsiveness, enhanced mucus secretion, airway eosinophilia, increased IgE synthesis, and elevated interleukin-5 levels in bronchoalveolar lavage that could be reversed with exogenous adenosine deaminase (6) has further strengthened the causal association between adenosine and an asthma phenotype. To further pursue mechanisms, Banerjee et al., report, in one of this issue’s articles in focus (Ref. 2, see p. L169), that in adenosine-deficient mice, a large number of genes are dysregulated in the lungs, many of which can be linked to the “asthmatic” changes reported in their earlier study. Of particular interest is their finding that vascular endothelial growth factor and monocyte chemotactic peptide-3 in the lung are also increased at the protein level. However, their elegant use of nucleic acid arrays also highlighted many other genes that could be relevant to asthma pathophysiology, including osteopontin, insulin-like growth factor-I, and fibronectin, with increases in the adenosine-deficient mice of 28-, 15-, and 6-fold, respectively. Along with the cathepsins
family of proteases (increased 2- to 8-fold), these adenosine-regulated molecules are more closely linked to the aberrant tissue injury and repair response, a recently recognized important component of chronic asthma (14). The use of cDNA gene array technology, followed by quantification of dysregulated genes and measurement of their protein products, as illustrated in this study, is a good example of how modern molecular-based methodology can be used to rapidly identify potential disease-related targets. However, in the final analysis, it is only when such methods are applied to human asthma that the significance of these fascinating findings in mice can be fully appreciated in relation to the disease in humans (19). The increased occurrence of eosinophilia and disordered lung function in adenosine deaminase-deficient humans (26) may lend itself to study in this way.

The recent discovery that adenosine also causes bronchoconstriction in chronic obstructive pulmonary disease, but only in those who exhibit evidence of eosinophilic inflammation in their airways (25), widens interest in this purine nucleoside as a mediator of lung disease. Even in asthma, it seems that the airway response to adenosine correlates more closely with disease activity than other more conventional forms of bronchial provocation (1, 12). Adenosine may also be linked to bronchoconstriction with exercise (10), a characteristic feature of asthma in children and young adults. Whether the proasthmatic effects of adenosine are mediated through the A(2B) receptor or not will have to await the introduction of selective antagonists for clinical trial. Until then, there is still much to be learned about the ubiquitous effect of this nucleoside on target cells in both normal and diseased airways.

REFERENCES