A role for neural pathways in adenosine-induced bronchoconstriction

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Adenosine is a widely distributed purine nucleoside that serves many roles in homeostasis and the cellular response to stress. As an extracellular signaling molecule, adenosine interacts with P1 purinergic receptors, known as the adenosine receptors, to regulate a vast array of cellular responses (9, 13). Almost 25 years ago, Cushing and colleagues (5) made the observation that inhaled adenosine could induce bronchoconstriction in asthmatics, although having essentially no effect in normal subjects. Subsequent analyses have gone on to verify adenosine as a potent bronchoconstrictor in various types of asthmatics (reviewed in Ref. 26) as well as in chronic obstructive pulmonary disease (COPD) (19). Bronchoconstriction is a prominent component of asthma, and the realization that adenosine has selective activity in this process within this patient population has fueled research efforts to identify the mechanisms involved with the goal of developing specific adenosine receptor analogs to be used in the diagnosis and treatment of asthma and perhaps COPD.

Research in a number of in vitro and in vivo model systems has explored mechanisms of adenosine-induced bronchoconstriction, and several hypotheses have emerged. One is that adenosine has a direct effect on airway smooth muscle contractility through actions of the A1 adenosine receptor (A1R) (1). Second, there is substantial evidence, particularly in humans, that adenosine-induced bronchoconstriction is secondary to the release of bronchoconstrictive mediators from airway mast cells (4, 8). The adenosine receptors involved in this process are still not clear, although the A2AR has been touted as important in human mast cell degranulation (11), whereas the A3R appears to predominate in rodents (28). The third potential pathway for adenosine-induced bronchoconstriction is through a neuronal mechanism (14, 17, 22). Neural-based mechanisms of adenosine-induced bronchoconstriction have received less attention than hypotheses centered on mast cells. In this issue of AJP-Lung, Hua and colleagues (12) use genetically modified mice to demonstrate that adenosine-induced bronchoconstriction in naïve animals is mediated by the A1R and involves the activation of sensory neurons. It is likely that in disease states, such as the asthmatic airway, multiple interacting mechanisms, including chronic inflammation and changes in airway structure, contribute to adenosine-induced bronchoconstriction. Nonetheless, the study by Hua et al. (12) provides new compelling evidence that A1R-mediated and neuronal pathways should be considered as a major pathway for adenosine-induced bronchoconstriction.

Experiments conducted in a variety of animal models including rabbits (6, 16), guinea pigs (14), rats (10), and mice (7) have demonstrated adenosine-induced bronchoconstriction following allergic sensitization. Furthermore, the use of pharmacological approaches in rabbits (6, 16) and guinea pigs (14) implicate the engagement of the A1R in these processes. This is supported further by in vitro experiments in humans where isolated bronchi from asthmatics exhibit increased constriction in response to adenosine relative to nonasthmatic bronchi, a response that appears to be mediated through an A1R mechanism (2). The ability to selectively remove genes from mice has provided a powerful means for testing the involvement of specific pathways in physiological processes in the whole animal. Hua and colleagues (12) demonstrate that naïve wild-type mice as well as naïve A2AR, A2BR, and A1R knockout mice all exhibit adenosine-induced bronchoconstriction, whereas naïve A1R knockout mice do not. These observations, together with the aforementioned findings in model systems and human asthmatics, strongly implicate A1R engagement in the regulation of adenosine-induced bronchoconstriction.

By using vagotomy as well as inhibitors of cholinergic pathways, Hua and colleagues (12) were able to demonstrate that neural reflexes are necessary for adenosine-induced bronchoconstriction in naïve mice. This finding suggests responses in mice may differ from other species with regard to adenosine-induced bronchoconstriction in that responses in other models (14) as well as humans (22) seem to require allergic sensitization. However, the neural findings in mice are consistent with those seen in asthmatics treated with neural inhibitors (22) and allergic guinea pigs given vagotomy or treated with atropine (14), where adenosine-induced bronchoconstriction was also attributed to neural activation. Thus activation of vagal nerve components through a mechanism that involves the A1R is likely an important mechanism in adenosine-induced bronchoconstriction in naïve mice and in allergic models and asthmatics. However, the exact mechanisms of adenosine-induced bronchoconstriction as pertains to what is seen in the inflamed airways of asthmatics are far from understood. Similarly, the involvement of other adenosine receptors in processes that affect airway inflammation and remodeling, which can in turn impact adenosine-induced bronchoconstriction, needs to be clarified.

Bronchoconstriction resulting from the release of mediators from mast cells is a mechanism that must be considered when trying to understand adenosine-induced bronchoconstriction in the inflamed lung. Compounds preventing mast cell degranulation can attenuate adenosine-induced bronchoconstriction in asthmatics (21), and treatment with compounds that block the activity of mediators released from mast cells such as histamine (24) and leukotrienes (23) can attenuate adenosine-induced bronchoconstriction. In further support for the involvement of mast cells, adenosine challenges can lead to increased levels of leukotrienes in the exhaled breath condensates from asthmatics (3), and adenosine can potentiate mediator release from human lung mast cells (20). Last, mast cell degranulation also serves a role in allergic models of lung disease in rats (10) and mice (18). Collectively, these studies argue for an indirect pathway for adenosine-induced bronchoconstriction in the asthmatic airway, which involves the degranulation of airway mast cells and the release of bronchoconstrictive agents. The
specific adenosine receptors involved in mast cell-driven bronchoconstriction are not clear; however, the A₁R appears to be the major receptor responsible for mast cell degranulation in the rodent (28), whereas the A₂B R may serve this function in the human mast cell (11).

Thus it is likely that adenosine-induced bronchoconstriction involves both neuronal pathways and mast cell degranulation, whereas direct effects on smooth muscle appear to be less clear. Furthermore, the relative contribution of neuronal and mast cell pathways to the regulation of airway tone in asthma will likely depend on disease state. One can envision that the severity of disease will impact multiple features such as inflammatory cell activity and the production of cytokines and other mediators that influence mast cell and neuronal activity. In addition, airway remodeling that occurs in more severe asthmatics will likely alter the responsiveness of these pathways to adenosine. The involvement of specific adenosine receptors in adenosine-induced bronchoconstriction in the context of these complex scenarios is not known but is likely being explored by a number of laboratories. As adenosine receptor knockout mice are subjected to models of allergic lung disease, their contribution to processes central to the regulation of airway disease will hopefully be clarified. To date, work in A₂B R knockout mice has revealed that genetic removal of the A₂B R, a well known anti-inflammatory signaling pathway, leads to enhanced airway reactivity following allergen challenge (15). In the context of the findings from Hua and colleagues, it will be interesting to determine the status of airway inflammation and reactivity to adenosine in A₁R knockout mice subjected to allergic stimuli.

Finally, when considering the role of adenosine signaling in diseases such as asthma and COPD, its bronchoconstrictive activities are only part of the story. Adenosine produced during inflammation and damage in the lung likely impacts a number of inflammatory and tissue remodeling processes that can impact disease. These may involve both tissue-protective and tissue-destructive effects that will likely be regulated by different adenosine receptors. For example, engagement of the A₂B R can promote the production of inflammatory mediators from mast cells that may influence the progression of disease (25). In support of this, an A₂B R antagonist is able to attenuate features of airway remodeling and fibrosis in adenosine-mediated lung disease (27), suggesting a role for this receptor in chronic phases of lung disease. Ultimately, observations in mice must be translated into humans, and it is likely that we will not completely appreciate the involvement of adenosine signaling in aspects of complex lung diseases such as asthma until trials in human asthmatics have been run using adenosine-based therapeutics such as A₁R or A₂B R antagonist.

REFERENCES

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