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Exercise-induced asthma and plasma adenosine: Is there a causative link?

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To the editor:

The recent article by Vizi et al¹ shows elevation in plasma adenosine during exercise-induced asthma (EIA) with significant associations with changes in FEV₁ and SaO₂. The authors speculated that the rise in plasma adenosine has a role in the development of EIA. However, it appears that the evidence to support these conclusions is not sound. Given that reduced oxygen availability is an important cause of adenosine production,² the authors' findings might simply reflect the relatively excessive adenosine production during bronchoconstriction. Therefore, elevation in plasma adenosine might be due to a nonspecific effect of hypoxia (as suggested by the relationship between decrease in SaO₂ and increase in adenosine levels) as a result of acute bronchoconstriction (as suggested by the relationship between degree of airway obstruction and increase in adenosine levels). Comprehension of the present findings could have been corroborated by a control experiment using methacholine-induced bronchoconstriction in the patients with asthma.

Interpretation of these results might also prove problematic because the control subjects in the study were nonatopic (whereas all of the asthmatic patients were atopic). Atopy by itself could have been a critical confounder in this investigation, as atopic airways might respond

more intensely to physical/osmotic stimuli, thus producing additional adenosine. Adenine nucleotides are present in large quantities in the cytoplasm of airway cells and then converted to adenosine by a plasma membrane 5'-nucleotidase.³ Given that higher adenosine concentrations have been demonstrated in the bronchoalveolar lavage fluid of subjects with asthma in comparison with nonatopic controls,⁴ it is conceivable that osmotic stimuli might elicit further adenosine release from activated/inflamed airway cells in asthma/atopy. To exclude the potential influence of atopy on adenosine production, a group of atopic control subjects should have been tested before and after exercise.

Vizi et al¹ would concur with us that it is unlikely that the increase in adenosine levels after exercise contributes to EIA, and this for 3 main reasons. First, it is well established that the contractile airway response that follows exercise in human asthma is mainly due to spasmogenic mediators released from immunologically primed mast cells by osmotic changes. Second, there is little evidence that human airway smooth muscle is a direct target of adenosine. Third, adenosine infusion for coronary vasodilation during perfusion scintigraphy was reported to cause bronchoconstriction in less than 2% of 117 patients with concomitant asthma or chronic obstructive pulmonary disease.⁵ It is obvious that definitive confirmation of the contributory role of adenosine in EIA will be established only through the use of potent and specific adenosine antagonists that are now in clinical development. For these reasons, the increase in adenosine levels after exercise, rather than representing a contributing factor in EIA, could be interpreted either as a nonspecific associated event or as an epiphenomenon.

Finally, the authors speculate that the increase in adenosine concentration enhances the effect of physical triggers activated by exercise in asthma. This would be acceptable if basal levels of adenosine were more elevated in the asthmatic subjects than in the controls. It is ironic that the data appear to challenge their hypothesis, inasmuch as basal levels of adenosine were not significantly different between the groups.

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