In the first Highlighted Topics article featured in this issue of the *Journal of Applied Physiology*, entitled “Hypersensitivity of pulmonary C fibers induced by adenosine in anesthetized rats,” Gu et al. explore the potential role of adenosine in the development of airway hyperresponsiveness. It is well recognized that activation of C-fiber sensory nerve endings in the airways and lungs elicits reflex responses such as bronchoconstriction, hypersecretion of mucus, and cough in various species including humans. Sustained stimulation of these sensory endings is also known to induce neurogenic inflammation in the airways via local release of tachykinins in rodents. Therefore, it is believed that hypersensitivity of these sensory nerves is involved in the manifestation of bronchial hyperreactivity. Adenosine is a purine nucleoside product of ATP metabolism and is produced by virtually all metabolically active cells, particularly when energy demand cannot be matched by oxygen supply, such as during tissue ischemia or inflammation. Published evidence has strongly suggested the involvement of adenosine as an inflammatory mediator in the pathogenesis of airway hyperresponsiveness. Indeed, high concentrations of adenosine have been detected in the bronchoalveolar lavage fluid of subjects with asthma, and the plasma level of adenosine doubles after antigen challenge is received in asthmatic patients. In this article, these investigators report evidence that a low dose of adenosine, which did not produce significant changes in the basal cardiovascular conditions, induced a pronouned and reversible sensitizing effect on pulmonary C-fiber endings in rats. The study by Gu and colleagues further demonstrates that this sensitizing effect of adenosine on the sensory endings is mediated primarily through the adenosine A₁ receptor. This finding lends additional support to the suggestion that adenosine contributes to the development of airway hyperresponsiveness and that the adenosine A₁ receptor plays a key role in this action. Whether this sensitizing effect of adenosine on the C-fiber endings is generated by a direct activation of the A₁ receptor expressed on the neuronal membrane of these sensory terminals or whether this involves releases of other mediators from intermediate cells (e.g., mast cells) requires further investigation.

In the second article featured in this issue, entitled “Airway contractility and smooth muscle Ca²⁺ signaling in lung slices from different mouse strains,” Bergner and Sanderson confirm that different mouse strains express variable amounts of airway contraction in response to similar stimulation. However, the Ca²⁺ signaling displayed by smooth muscle cells in all three mouse strains examined was similar with respect to the initial transient elevation and frequencies of subsequent Ca²⁺ oscillations. These investigators conclude that, in the absence of inflammation, airway hypercontractility might reside with changes in Ca²⁺ sensitivity of the contractile machinery or changes in lung compliance rather than with changes in Ca²⁺ signaling itself. The discovery of mice with hyperreactive airways, which may serve as an animal model, is important to asthma research because these mice provide researchers the opportunity to investigate the basic mechanisms of airway reactivity in the absence of inflammation. Although it is known that an increase in intracellular Ca²⁺ is essential for smooth muscle contraction, the details of this process and its relationship to small airway narrowing is not well understood. Recently, these investigators developed a technique to visualize intracellular Ca²⁺ signaling in smooth muscle cells of small airways by using thin lung slices and confocal microscopy. Using this technique, Bergner and Sanderson investigated Ca²⁺ signaling in small airway smooth muscle cells from three different mouse strains that represent the full range of airway reactivity. There are two phases in the Ca²⁺ signaling induced by acetylcholine in airway smooth muscle cells: 1) an initial phase consisting of a transient elevation in intracellular Ca²⁺ during which contraction is initiated and 2) a second phase consisting of Ca²⁺ oscillations that maintains the contracted state. The frequency of Ca²⁺ oscillations correlates with the magnitude of contraction, and the loss of the Ca²⁺ oscillations results in relaxation of airway smooth muscle cells.

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