Where to from Here for Exercise-Induced Bronchoconstriction

The Unanswered Questions

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KEYWORDS

• Injury • Epithelium • Water transport • Mast cells • Sensory nerves • Eicosanoids

KEY POINTS

- Injury of the epithelium is important in the development of exercise-induced bronchoconstriction (EIB).
- Airway injury in elite athletes may relate to the large volumes of air inspired during training.
- Dysregulation of water movement and balance in the airways may contribute to the pathology of EIB.
- Mast cells, eosinophils, and sensory nerve cells are all likely to be involved in EIB.
- Cysteinyl leukotrienes are the major mediators of EIB with prostaglandins (PGs) likely to play a role in attenuating (PGE_2) or enhancing (PGD_2) the response.
- Refractoriness after exercise may relate to desensitization of airway receptors rather than depletion of mediators.
- New and more sensitive technologies for assaying mediators and measuring changes in pulmonary function are becoming available and will improve our understanding of EIB.

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- Mild EIB may represent a different phenotype than more severe EIB and involve different mechanisms.
- EIB in children has faster onset and recovery compared with adults and the mechanism for this may relate to remodeling.

WHAT IS THE ROLE OF INJURY OF THE EPITHELIUM IN EXERCISE-INDUCED BRONCHOCONSTRICTION?

In recent years, a concept has emerged placing an abnormal airway epithelium at the center of asthma development and progression.[1,2] In asthmatic patients, properties of the epithelial barrier are believed to be impaired as a result of both intrinsic (eg, genetic polymorphisms)[3] and environmental factors (such as respiratory viruses, cigarette smoke, pollution, and allergens).[4–7] Susceptibility of the epithelium to damage by environmental agents followed by incomplete repair is believed to lead to a dysregulated repair process, with secretion of biologically active substances that drive the structural and inflammatory changes characteristic of asthma.[8] *In vitro* studies have recently confirmed that (1) the bronchial epithelial barrier in asthma is compromised (facilitating penetration of allergens and other noxious airborne particles) and (2) bronchial epithelial cells from asthmatic patients are inherently dysfunctional in their ability to repair wounds.[9,10] Whether these pathologic changes can be observed specifically in the airways of patients with exercise-induced bronchoconstriction (EIB) is not known; however, the number of ciliated epithelial cells shed into the airway lumen is higher in patients with asthma who have EIB.[11]

Although 10% of the population have EIB, this percentage is higher in elite athletes, making it one of the most common morbidities in this group.[12] High minute ventilation in conditions with dry air and a high pollen count may be factors that increase the incidence of EIB.[13–15] There is a connection between the incidence and the number of training years and intensity of the sport[16] suggesting that repetitive injury may play a role. It has been proposed that repetitive epithelial injury and the repair process that follows in elite athletes contributes to the development of EIB, possibly as a result of a change in contractile properties of the bronchial smooth muscle.[17,18]

Previous investigations *in vivo* based on indirect measures of airway epithelial integrity (ie, the concentration of columnar epithelial cells in induced sputum) suggest that injury to the airway epithelium is a key susceptibility factor for asthma with EIB.[19] Animal-based[20,21] and human-based studies[11,22–24] suggest that exercise hyperpnoea can lead to a transient loss of the integrity of the airway epithelial barrier. However, confirmation is required on whether the airway epithelium of patients with EIB (with and without asthma) is structurally and functionally abnormal.

Support for a central role of injury of the airway epithelium in EIB is important in that it may prompt a novel therapeutic approach to treatment. Whereas the currently recognized treatments for EIB (eg, inhaled β_2-agonists and inhaled corticosteroids [ICS]) act mainly downstream from the airway injury (regulating the inflammatory process, mucus secretion, and airway hyperresponsiveness), drugs that help to restore normal epithelial function could potentially prevent the inception of the disease and/or alter its course. New therapeutic agents possibly include drugs such as epidermal and keratinocyte growth factors that enhance the ability of the epithelium to withstand environmental challenge and/or to restore the barrier functions.[25,26]