

Pathogenesis of Exercise-Induced Bronchoconstriction

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KEYWORDS

- Hyperpnoea • Osmotic stress • Thermal stress • Epithelial injury
- Airway inflammation

KEY POINTS

- The increased ventilatory demand associated with exercise is a major determinant in exercise-induced bronchoconstriction (EIB).
- In susceptible individuals, the drying and cooling of the intrathoracic airways secondary to increased ventilatory flow trigger a cascade of events that ultimately leads to airway narrowing.
- This cascade of events may include epithelial injury, inflammatory mediator release, vasculature hyperemia, and/or sensory nerve activation.
- A dysfunctional airway epithelium, either inherited or acquired, is thought central in the long-term development or progression of EIB.
- Environmental factors interacting with genetic predispositions modulate the airway response to exercise and contribute to the complex nature and pathogenesis of EIB.

INTRODUCTION

Exercise-induced bronchoconstriction (EIB) is defined as a transient airway narrowing that occurs shortly after strenuous exercise. EIB is highly prevalent in individuals with clinical asthma but can also occur in otherwise healthy individuals. Because exercise is unavoidable at times, and sudden bronchoconstriction triggered by exercise can be fatal,¹ understanding the mechanisms for EIB is a prerequisite for developing effective strategies for its prevention and treatment.

While exercise is recognized as a potent trigger for bronchoconstriction, it is not the exercise per se that is directly responsible for the airway narrowing, but rather the hyperpnoea associated with it. When people exercise, the ventilatory demand

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increases from ~ 6 L/min at rest to >200 L/min in elite endurance athletes, and there is a shift from nasal to mouth breathing. As a consequence, the need to heat and humidify the inhaled air is increased, and abnormal heat and water losses occur within the lower airways. The thermal and osmotic stresses generated by this loss trigger a wide range of vascular, cellular, and neural events, ultimately leading, in susceptible individuals, to airway narrowing. At times of increased ventilatory flow, the mechanical load applied to the airways is increased, and this event could promote airway epithelial injury. Complex interactions between genetic and environmental factors (eg, air pollutants, allergens, and viruses) are likely to modulate the extent of the injury. The consequences of a disrupted airway epithelium are, in the short-term, to facilitate the passage of noxious substances across the airway wall; in the long-term (through repetitive and/or aberrant injury-repair), the possible development of airway hyper-responsiveness (AHR) and tissue remodeling. While there is a theoretical base for the involvement of parasympathetic and neurogenic factors in EIB, human-based evidence is still lacking to confirm the contribution of the nervous system to the pathogenesis of EIB.

EIB OR EXERCISE-INDUCED ASTHMA?

EIB is identified as a transient reduction in lung function after exercise in individuals with or without clinically recognized asthma. A 10% or more decrease in forced expiratory volume in 1 second (FEV_1) after strenuous exercise is widely accepted as evidence for EIB.² The term exercise-induced asthma (EIA) describes the same functional change in those with a prior diagnosis of asthma. Both EIB and EIA are typically associated with respiratory symptoms. Yet occurrence of symptoms is not systematic and should not be relied upon for diagnosis.^{3,4} The generic term EIB will be used in this article.

The prevalence of EIB is usually estimated around 30% to 50% among individuals with asthma. While EIB is often just one of the many manifestations of asthma, the severity of asthma seems to act as a contributing factor. In a study performed on 164 children with asthma, the prevalence of EIB was greater in those children with moderate or severe persistent asthma (as defined by the Global Initiative for Asthma guidelines) compared with those with intermittent asthma.⁵ EIB in childhood has also been suggested as predictor for subsequent development of asthma.⁶ However, studies that have assessed EIB in childhood as a risk factor for asthma symptoms in early adulthood have so far produced variable outcomes.⁶⁻⁹

Alongside children,^{5,10} populations of regular exercisers, such as elite athletes¹¹ and active-duty military recruits,¹² seem particularly at risk for EIB. In Olympic athletes, EIB has been identified as the most common chronic medical condition, with a prevalence rate of $\sim 8\%$.¹³ While regular exercisers often report the same symptoms as asthmatic individuals on exertion (ie, breathlessness, mucus production, wheezing, cough, and chest tightness),¹⁴ exercise is typically the unique trigger for the airway narrowing and respiratory symptoms in these individuals; therefore EIB is the preferred terminology.

ROLE OF THERMAL STRESS IN EIB

During strenuous exercise, the heating of large volumes of unconditioned air to body temperature is associated with a reduction in the temperature of both the intrathoracic and intrapulmonary airways.¹⁵ Originally, airway cooling was proposed as the stimulus to EIB.¹⁶ This proposal was extended in 1986 to encompass the bronchial vasculature and became known as the thermal theory of EIB.¹⁷ It was proposed that the cooling

effect of exercise hyperpnoea causes vasoconstriction of the bronchial circulation. As the exercise ceases and ventilation returns to normal, a reactive hyperemia occurs, leading to vascular leakage and edema formation. The thermal theory proposed that it was the vascular engorgement and edema in the mucosa and submucosa that accounted for the transient airway narrowing of EIB.¹⁸

Some studies,¹⁷ but not all,¹⁹ have shown that the fall in FEV₁ that followed a short period of hyperpnoea was directly linked to the rate of change in ventilation after the challenge and to the thermal gradient after challenge. Further, a reduction in mucosal blood supply induced by inhalation of norepinephrine was accompanied by limited airway rewarming and by an attenuated airway response.²⁰

While thermal stress is likely to contribute to EIB in low temperature conditions, thermal stress is not a prerequisite for EIB. For example, severe EIB has been shown to occur when hot dry air is inspired.^{21–24} Moreover cooling the inspired air, while keeping water loss the same, did not necessarily enhance severity of EIB.²⁵ When the air inspired during exercise is cold, both the thermal and osmotic stresses are likely to be important; first, because inspiring cold air increases the surface area that becomes dehydrated and hyperosmotic, and second because vascular engorgement could amplify the airway narrowing effect of smooth muscle contraction.²⁶ These events may account for the increased severity of EIB observed in athletes when exercising in the cold.^{27,28}

OSMOTIC STRESS AS A PREREQUISITE FOR EIB

The osmotic theory was developed as a consequence of the observations of severe EIB with hot dry air inspire.^{21–23,26} It was proposed that the airway surface liquid (ASL) volume was so small (<1 mL in the first 12 generations of airways) that the evaporative loss in humidifying the air during exercise led to a transient dehydration and increase in ASL osmolarity.^{29,30}

According to the mathematical model developed by Daviskas and colleagues,³¹ with air of temperate conditions and ventilatory flows of 60 L/min, generations 8 to 10 are recruited in the conditioning process, and a significant amount of water is lost within these small airways (**Fig. 1**). During real-life exercise, individuals often reach ventilatory flows >60 L/min⁻¹, and environmental conditions (such as cold dry air) can exacerbate water loss within the airways. In those situations, even the very small airways (generations 10–12) could be subject to dehydration.

The osmotic theory of EIB proposes that the dehydration of the ASL triggers a cascade of events that involves sequentially: a rise in the osmolarity of the ASL; initial water movement from the surrounding cells toward the airway lumen to rapidly restore the ASL (**Fig. 2**); then the shrinkage of subepithelial cells; release of bronchoconstrictive inflammatory mediators (eg, leukotrienes, prostaglandins, or histamine) during regulatory volume increase; and, in the presence of hyperresponsive airway, bronchial smooth muscle contraction (**Fig. 3**). It is the loss of water from the airway surface and its consequences that is common to both theories, but only the osmotic theory encompasses the release of mediators.

A large body of evidence supports the osmotic theory.²⁶ The severity of EIB was linked to the water content of inspired air³² and to the measured water loss at the mouth.²⁹ The airway response to exercise was significantly blunted in asthmatics when air preconditioned to body temperature and fully saturated with water vapor was inspired.^{29,32} The mast-cell stabilizing agents nedocromil sodium and sodium cromoglycate are known to inhibit the obstruction that follows exercise³³ and hyperpnoea of dry air.^{34,35} Inhalation of the osmotic agent mannitol can mimic the effects of exercise

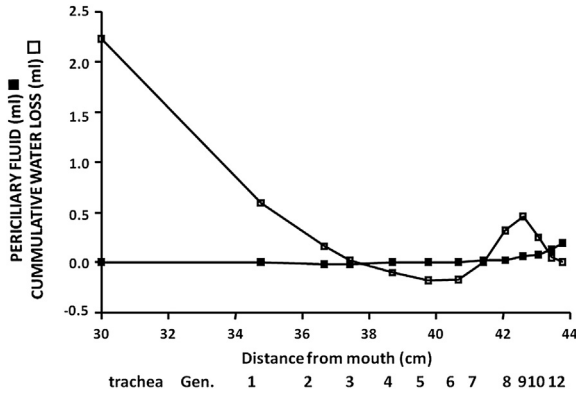


Fig. 1. Cumulative loss of water predicted for each generation from the model of Daviskas³¹ under inspiratory conditions of approximately 26°C with 8.8 $\mu\text{L H}_2\text{O/L}$ of air (36.5% relative humidity) and for a rate of ventilation of 60 L/min sustained over 8 minutes. The periciliary fluid volume available is also illustrated. The volume of water lost in 8 minutes exceeded the volume of periciliary fluid available in most generations. (*Data from Anderson SD, Daviskas E, Smith CM. Exercise-induced asthma: a difference in opinion regarding the stimulus. Allergy Proc 1989;10:222.*)

on the airway caliber^{36,37} and the inflammatory mediator release in asthmatics.^{38,39} Athletes in whom dehydration of their airways is more likely to occur (ie, endurance-trained athletes and winter athletes) are at increased risk for EIB.¹¹

Recently, it has been suggested that impairment in bronchial airway surface secretions could contribute to dehydration of the ASL during exercise in patients with asthma and in athletes. Using sputum percent solids as a marker for airway hydration, Loughlin and colleagues reported that airway hydration is significantly reduced at baseline in clinically stable asthmatics.⁴⁰ Further, athletes with excessive bronchial reactivity have been found to have a reduced ability to sweat.⁴¹ Since respiratory gland epithelium and sweat gland epithelium share identical mechanisms of muscarinic receptor (m3 subtype)-dependent sodium, chloride, and water secretion, this latest result may indicate a general deficiency in body fluid homeostasis regulation in those individuals with EIB. From a mechanical viewpoint, mice deficient with aquaporin 5, a water channel protein expressed in alveolar type 1 cells of the lungs, appear hyper-reactive to bronchoconstriction.⁴² Further studies are required to confirm the role of aquaporin 5 in the pathogenesis of EIB in humans.

EPITHELIAL DISRUPTION AS A CONSEQUENCE OF THE THERMAL STRESS

The volume of ASL is critical for proper lung defense. When the depth of the ASL is reduced, the integrity of the epithelial barrier is compromised, and epithelial cell injury is likely to occur. In animals, hyperventilation of dry air has been shown to cause significant desquamation of the airway epithelium,^{43,44} with the extent of injury being dependent upon ventilatory flow and dryness of the air.⁴⁵ In asthmatic individuals with EIB, induced sputum samples obtained after exercise revealed significant airway damage, with an increased concentration of columnar epithelial cells that correlated with the release of the inflammatory mediators histamine and leukotrienes.⁴⁶ Using the lung-specific protein Clara cell CC16 as an index for airway permeability, the authors^{47,48} and others^{49,50} confirmed that strenuous exercise transiently compromises the integrity of the airway epithelial barrier.

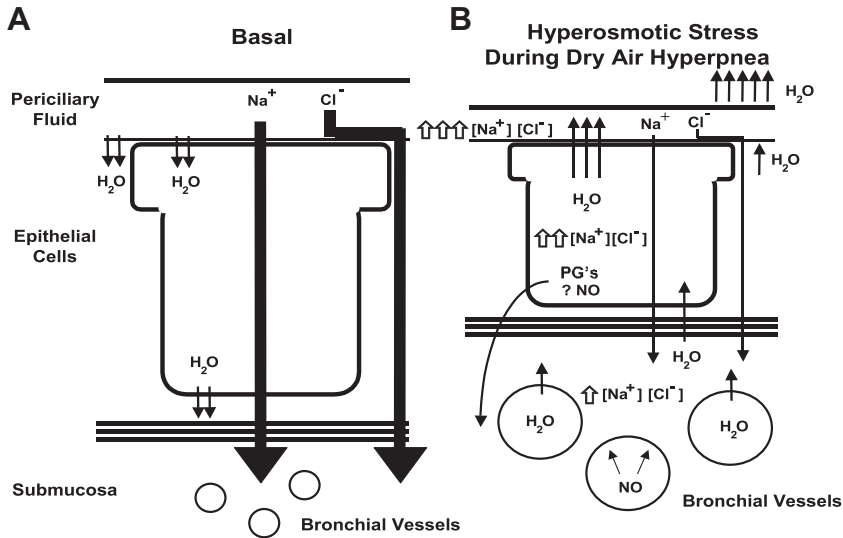


Fig. 2. Epithelial cells and ion transport under basal conditions (A) and hyperosmotic stress during dry air hyperpnea (B). Under basal conditions, Na^+ ions are absorbed via an apical sodium channel, and Cl^- ions move paracellularly. Under basal conditions, water moves into the epithelial cells and submucosa due to the osmotic gradient created by the movement of these ions. During hyperpnea, evaporative water loss reduces the periciliary fluid layer and increases the ion concentration, which creates an osmotic stimulus for water to move out of the epithelial cells. As a result, the epithelial cells shrink, creating an osmotic stimulus for water to move from the submucosa. Hyperosmolarity of the epithelial cells and the submucosa is a possible stimulus for the release of nitric oxide (NO) and prostaglandins (PGs). These substances may contribute to the increase in the blood flow documented in people breathing dry air. (From Anderson SD, Daviskas E. Airway drying and exercise-induced asthma. In: McFadden ER, editor. Exercise-induced asthma—lung biology in health and disease. New York: Marcel Dekker; 1999. p. 91; with permission.)

In the short term, breaches in the airway epithelial barrier could, among other events, transiently facilitate the passage of inhaled substances (ie, viruses, bacteria, allergens, or airborne pollutants or irritants) across the airway epithelium and increase the interaction of those substances with resident immune and inflammatory cells, trigger an inflammatory response with consequent infiltration of mast cells⁵¹ and secondary influx of neutrophils,⁴⁹ cause the loss of the bronchoprotective agent prostaglandin E_2 ,^{46,52} and impede mucociliary clearance.⁵³ Either alone or in combination, these factors could initiate acute airway narrowing following exercise.

DOES MECHANICAL STRESS CONTRIBUTE TO AIRWAY INJURY?

Although dehydration stress is regarded as the most important precursor of airway epithelial injury during exercise, the role of mechanical stress cannot be excluded.

During respiration, the airways are subjected to complex physical forces. Movement of air across the surface of the airway imparts a shear stress on the surface epithelium. Mathematical modeling has shown that at a peak flow rate of 1 L/s (representing normal expiratory flow), wall shear stress in the major airways reaches up to 0.9 Pa.⁵⁴ At 8 L/s (representing cough), the maximum value for wall shear stress rises to 19 Pa.⁵⁴ Cough, through wall shear stresses, is thought to be a contributing factor to

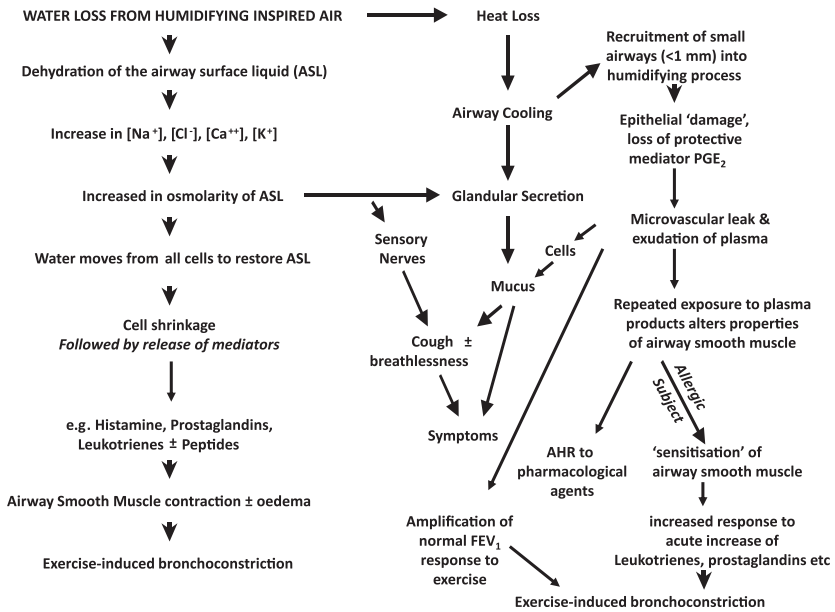


Fig. 3. Flow chart describing the acute events leading to EIB in the classic asthmatic (*left*) and the events leading to the development of EIB in the athlete (*right*). (From Anderson SD, Kippelen P. Exercise-induced bronchoconstriction: pathogenesis. *Curr Allergy Asthma Rep* 2005;5:117; with permission.)

airway injury, inflammation, and obstruction.⁵⁵ During exercise, the increased osmolarity of the ASL is likely to activate sensory nerves and trigger cough.⁵⁶ Cough on exertion is often considered as a clinical manifestation of asthma. Moreover, cough is commonly reported by elite athletes,⁵⁷ especially during the winter months.⁵⁸ Hyperpnoea of cold air is known to stimulate cough.⁵⁹ Cough, through wall shear stresses, may therefore contribute to the high prevalence of AHR, inflammation, and remodeling in cold-weather athletes.^{60,61}

During exercise, stretching of the airway wall and steeper transairway pressure gradients could cause deformation of the epithelial cells. Mechanical deformation of epithelial cells is accompanied by signaling, structural, and mechanical responses⁶² that may impact on airway function and cause additional trauma to an already inflamed epithelial layer. However, high physical forces are not all bad for the airways. Deep breaths, as occurs spontaneously with exercise, are regarded as among the most potent bronchodilator agents.⁶³ In healthy individuals, deep breaths are thought to help to maintain airway patency through disruption of the force-generating machinery (ie, detachment of cross bridges). In asthmatics, however, the bronchodilator effect of tidal breathing muscle stretches is often lost.⁶⁴ As a consequence, the onset of EIB may sometimes occur during exercise in patients with asthma.^{65,66}

EPITHELIAL INJURY IN THE DEVELOPMENT OF EIB

In the long term, interaction between a disrupted airway epithelium and environmental stimuli could lead to functional and structural changes within the airways.

To restore the integrity of the airway epithelial barrier and maintain homeostasis, injury is rapidly followed by repair. The injury–repair processes are known to produce,

by themselves, a series of physiologic and cellular events within the airways that promote inflammation and tissue repair. An immediate response to the denudation of the airway epithelium *in vivo* is plasma exudation.⁶⁷ Strong secretory and exudative responses ensure that a gel-like network of fibrin and other attached proteins covers the denuded basement membrane, which then helps to maintain mucosal defense and assist in the restoration process.⁶⁷ In parallel, de-differentiation and migration of basal and Clara cells ensure a rapid restoration of the epithelium.⁶⁸ Rapid and well-orchestrated injury–repair processes are critical in ensuring that the airway epithelium keeps protecting the internal milieu from external noxious agents.

During exercise hyperpnoea, the exposure of the airways to environmental stimuli is increased. In the presence of environmental triggers and with a susceptible airway epithelium (such as in asthma), not only does penetration of external noxious agents increase, but aberrant repair may also occur. A defect in epithelial tight junctions has recently been observed in patients with asthma.⁶⁹ Moreover, an *in vitro* study has implicated a decreased production of fibronectin (ie, 1 of the primary extracellular matrix proteins) in dysregulated repair of asthmatic epithelium.⁷⁰ A dysregulated (or aberrant) repair may lead, among other things, to the generation of growth factors and to an ineffective resolution of inflammation (with increased cytotoxicity).⁷¹ Through interaction with the underlying mesenchyme, growth factors and cytokines could then promote tissue remodeling and persistent inflammation (Fig. 4). In asthma with EIB, airway epithelial injury has been observed at rest,⁵² and exercise has been shown to exacerbate the degree of airway injury.⁴⁶

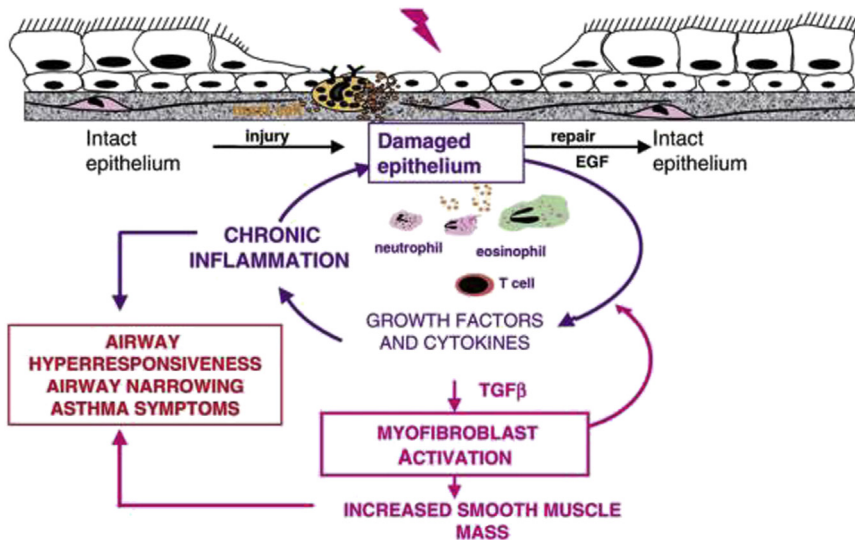


Fig. 4. Model for the interaction between environmental agents and a susceptible epithelium as a trigger for persistent airway inflammation and remodeling in asthma. Susceptibility to environmental oxidants causes epithelial damage, which triggers a normal injury–repair response involving release of mediators that promote inflammation and tissue repair (which involves transient remodeling responses). However, the release of endogenous oxidants by inflammatory cells causes further injury to the susceptible epithelium, resulting in a chronic state of tissue damage, which maintains the appropriate environment for persistent inflammation and tissue remodeling. (From Davies DE, Holgate ST. Asthma: the importance of epithelial mesenchymal communication in pathogenesis. Inflammation and the airway epithelium in asthma. *Int J Biochem Cell Biol* 2002;34:1524; with permission.)

In a susceptible airway epithelium, the inflammatory cell influx that follows tissue injury may also initiate secondary damage through production of endogenous reactive oxygen.⁷¹ In asthmatic children and adolescents with EIB levels of 8-isoprostane in exhaled breath condensate are increased.⁷² Moreover, an increase in the body's antioxidant capacity through supplementation with undenaturated whey protein⁷³ or ascorbic acid⁷⁴ has been shown to significantly reduce the severity of EIB.

In nonasthmatic individuals whose airways are repetitively exposed to injury (such as elite athletes), rather than aberrant repair, it is the high frequency of the injury–repair process that could favor the development of EIB. In this population, transient but repeated leakage of bulk plasma could, via chronic exposure of the airway smooth muscle to biologically active molecules (eg, growth factors and cytokines), modify the contractile properties of the muscle, rendering it hyper-responsive (see **Fig. 3**). High prevalence of AHR has been observed in many elite athletes, particularly in those sustaining high ventilatory flows (ie, endurance-trained athletes) or those exposed to cold dry air (ie, winter athletes) or to noxious environmental conditions (eg, swimmers).^{11,75–77} Moreover, atopy is a strong risk factor for EIB in elite athletes.⁷⁸ In athletes with allergies, repeated injury–repair could create a model of passive sensitization,⁷⁹ whereby the smooth muscle would be repetitively exposed to circulating immunoglobulin E (IgE) and would promote the development of EIB (see **Fig. 3**).

CONTRIBUTION OF THE NERVOUS SYSTEM IN EIB

Parasympathetic innervation of the human airways regulates many aspects of airway function, including bronchial smooth muscle contraction, mucus secretion, and vasodilatation of the bronchial vasculature, all of which are involved in EIB. Through activation of muscarinic receptors present on extraneuronal cells, such as epithelial cells and inflammatory cells,⁸⁰ parasympathetic signaling may also contribute to airway inflammation and tissue remodeling.^{81,82} Thus far, however, the evidence for the involvement of the cholinergic system in EIB, via the use of the inhaled anticholinergic agent ipratropium bromide, has been conflicting.^{83–86} Moreover, the therapeutic effect of ipratropium on EIB seems to vary greatly among individuals.⁸⁷ This high variability has been attributed to interindividual differences in vagal activity.⁸⁸ Vagal activity is known to increase in endurance-trained athletes,⁸⁹ and endurance athletes are particularly prone to EIB.¹¹ Therefore it cannot be excluded that, in regular exercisers, the cholinergic system contributes to the development EIB.⁹⁰

Both chemical agents and physical factors (such as mechanical probing, dry gas hyperpnoea, and hypertonic aerosols) have the potential to activate sensory nerves endings from bronchopulmonary C-fibers and trigger the release of sensory neuropeptides (eg, substance P, neurokinin A, and calcitonin gene-related peptide).⁹¹ In animals, sensory neuropeptides have been shown to directly modulate bronchial tone, bronchovascular caliber and permeability, and secretions.⁹¹ These effects seem mainly mediated by the interaction between sensory neuropeptides substance P and neurokinin A with tachykinin (NK₁, NK₂) receptors, as demonstrated in patients with asthma.⁹² However, thus far, limited human-based evidence supports the role of sensory neuropeptides in EIB. The inhalation of the selective NK₁ receptor antagonist FK-888 before exercise in asthmatic patients did not inhibit EIB.⁹³ However, the recovery from EIB was somewhat accelerated with FK-888, which led the authors to postulate that NK₁ receptor-mediated mechanisms are involved in the recovery phase of EIB.

A novel theory is that, in asthmatic individuals, bronchoconstriction and mucus release after exercise could be partly mediated by retrograde axonal transmission

via neurokinin A release.⁹⁴ The theory proposes that, in the presence of an osmotic stress (such as during exercise), the disrupted airway epithelium of asthmatic patients with EIB causes sustained production of inflammatory eicosanoids, particularly cysteinyl-leukotrienes (cys-LTs). Cyst-LTs then activate sensory nerves containing neurokinins, which, in turn, initiate contraction of the bronchial smooth muscle and release of mucin. Significant release of de novo synthesized eicosanoids has been noticed in vitro following osmotic challenge of human mast cells.⁹⁵ Moreover, production of cys-LTs is known to be increased in asthmatic patients with EIB.^{52,96} Recently, in asthmatic patients with EIB, exercise was associated with increased release of goblet cell mucin 5AC (MUC5AC) and of cyst-LTs into the airways.⁹⁷ In the same study, levels of cyst-LTs in induced sputum were positively correlated with levels of neurokinin A.⁹⁷ Altogether, these results support the idea that neurokinin A release through sensory nerve activation may partly mediate contraction of the airway smooth muscle and overproduction of mucus in EIB.

SUMMARY

EIB occurs in individuals with and without clinically recognized asthma. EIB is a functional consequence of the overwhelming of the humidifying process of the airways during exercise. Loss of water associated with exercise hyperpnoea leads to a rise in the osmolality of the ASL, which causes inflammatory cells to release mediators of bronchoconstriction. During exercise in the cold, the loss of heat associated with hyperpnoea may lead to vascular engorgement as the airways rewarm after exercise and may precipitate or enhance airway narrowing. The multiple stressors (ie, heat, osmotic and mechanical stress) to which the airway wall is exposed during exercise are thought to cause injury to the airway epithelium and to trigger an injury–repair cascade. In individuals with a particular genetic make-up (eg, asthmatic individuals), aberrant repair of the airway epithelium could promote airway remodeling responses and a chronic and persistent inflammatory response, leading to EIB development/progression. In regular exercisers, it is the repetitive nature of the injury–repair processes that is thought, via release of bioactive substances, to change the contractile properties of the smooth muscle and induce AHR and promote EIB. Strategies to provide protection to the airways against environmental insults and/or to enhance the ability of the epithelium to withstand stresses during exercise should be devised to limit development/progression of the disease.

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