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New Insights into to Pathogenesis of Exercise-induced Bronchoconstriction

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Abstract

Purpose of review—Exercise-induced bronchoconstriction (EIB) refers to acute airflow obstruction that is triggered by a period of physical exertion. Here we review recent findings about the epidemiology of EIB, immunopathology leading to EIB, and the latest understanding of the pathogenesis of EIB.

Recent findings—Longitudinal studies demonstrated that airway hyperresponsiveness to exercise or cold air at an early age are among the strongest predictors of persistent asthma. Patients that are susceptible to EIB have epithelial disruption and increased levels of inflammatory eicosanoids such as cysteinyl leukotrienes (CysLT)s. The leukocytes implicated in production of eicosanoids in the airways include both a unique mast cell population as well as eosinophils. A secreted phospholipase A_2 ($sPLA_2$) enzyme that serves as a regulator of CysLT formation is present in increased quantities in asthma. Transglutaminase 2 (TGM2) is expressed at increased levels in asthma and serves as a regulator of $sPLA_2$-X. Further, $sPLA_2$-X acts on target cells such as eosinophils to initiate cellular eicosanoid synthesis.

Summary—Recent studies have advanced our understanding of EIB as a syndrome that is caused by the increased production of inflammatory eicosanoids. The airway epithelium may be an important regulator of the production of inflammatory eicosanoids by leukocytes. Abstract word count: 199

Keywords

Asthma; Eicosanoid; Eosinophil; Exercise-induced bronchoconstriction; Leukotriene; Mast Cell; Phospholipase; Prostaglandin; and Transglutaminase 2

Introduction

Exercise-induced bronchoconstriction (EIB) is a syndrome where a brief period of exercise or increase in ventilation triggers airflow obstruction that lasts 30 to 90 minutes in the absence of treatment. Although EIB occurs predominantly among patients with established asthma, there is evidence from cross sectional studies that only a portion of patients with asthma have EIB when tested with a specific challenge test. For example, in Algeria the prevalence of EIB was 47% among children with established asthma (1). These data are consistent with the largest prior study that established a prevalence of EIB of 46% out of 164 asthmatic children (2). Also consistent with prior studies (3), the Algerian study also found that 13.9% of children without a history of asthma had EIB (1). In accord with smaller

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studies showing that EIB identifies children at risk for chronic asthma, two recent large cohort studies have extended these findings. Parent reported exercise induced wheeze and a history of atopy were the strongest predictors of asthma over at least 6 years of longitudinal follow-up among 628 children who were evaluated prior to the age of 5 (4). In a longitudinal birth cohort that included follow-up data on 849 children, airway hyperresponsiveness (AHR) to cold dry air hyperpnea was associated with a increased odds ratio of 4.5 of asthma at 22 years of age (5).

EIB is a prototypical manifestation of indirect AHR similar to the airway response to hypertonic aerosols, eucapnic voluntary hyperpnea (EVH) and adenosine, but is only weakly related to baseline lung function or direct airway responsiveness to histamine or methacholine (6). However, several recent population-based studies in patients with symptoms of asthma have found that tests of indirect and direct AHR hyperresponsiveness perform similarly as screening tests (7, 8). Among 509 adolescents and adults with signs and symptoms of asthma, the sensitivity of mannitol to identify EIB was 59% and for methacholine was 56% (7); the prevalence of EIB in the study population was 43.5%. In a population of 99 children with suspected asthma, 21% of whom had EIB, the positive and negative predicted value of mannitol challenge for EIB were 68% and 89% (8).

The abnormal distribution of alveolar ventilation (Va) and perfusion (Q) that occurs during EIB can lead to arterial hypoxemia during exercise. Images of the airways during EIB obtained by hyperpolarized helium demonstrate areas of closure or near closure of segmental airways of the lungs during EIB (9). Of interest is a recent comparison of exercise- and mannitol-induced bronchoconstriction demonstrating that Va/Q imbalance was more pronounced in EIB than mannitol-induced bronchoconstriction, but there was less hypoxemia because of the residual increase in ventilation after exercise (10). The danger of bronchoconstriction triggered by exercise was highlighted several years ago by a population-based study that found 61 of 263 sports-related fatalities in young adults were caused by asthma exacerbation (11).

Pathophysiological determinants of EIB

Collectively, the epidemiology of EIB indicates that patients with this disorder represent a discrete phenotype. Whether or not this phenotype is a durable clinical phenotype awaits further longitudinal epidemiological studies. One recent study found that increased bronchodilator response is associated with asthma symptoms during exercise suggesting that subjects with more variability in airway tone may be more susceptible to EIB (12). In another very provocative study, the authors related pilocarpine-induced sweat secretion with methacholine reactivity and found that subjects with a negative methacholine challenge had more salivary secretion and higher sweat rate (13). Since prior studies have found that the rate of water transfer out of the airways is a major determinant of the severity of bronchoconstriction after exercise challenge, these findings suggest that the there may be an alteration in water handling by the airway epithelial surface. It is also recognized both humans and in animal models that dietary salt is a modifier of the severity of EIB (14), also possibly indicating a alteration in water handling by the epithelium. In line with evidence that the epithelium may play a major role in this disorder is that the number of airway epithelial cells shed into induced sputum is substantially higher among asthmatics with EIB compared to asthmatics without EIB (15).

The intensity of cellular airway inflammation and the generation of inflammatory mediators, particularly eicosanoids (i.e products of arachidonic acid) such as leukotrienes have been associated with the susceptibility to EIB (15, 16). Although sputum eosinophilia *per se* does not appear to be required for EIB, several prior studies have associated the degree of sputum

eosinophilia with the severity of EIB. A recent study of the inhaled corticosteroid (ICS) ciclesonide further refined these observations by demonstrating that the magnitude and onset of the suppression of EIB in response to high dose but not low dose ICS therapy was associated with the degree of sputum eosinophilia (17). Patients without sputum eosinophilia were less likely to have an improvement in EIB on an ICS (17). Mast cell infiltration of the airways has also been implicated in EIB. In a genome-wide expression study of airway cells, the expression of the mast cell genes tryptase and carboxypeptidase A3 (CPA3) were significantly increased in EIB positive asthmatics (18). This intraepithelial mast cell phenotype with high expression of tryptase and CPA3, but low expression of chymase was recently described in the Th2 high molecular phenotype of asthma (19, 20). Since this Th2 high phenotype is IL-13 driven (21), it is interesting to note that a genetic study found an association between IL-13 gene polymorphisms and the severity of EIB, and with the response to a leukotriene receptor antagonist (LTRA) among these subjects with EIB (22).

Several studies have noted an increase in the concentration of cysteinyl leukotrienes (CysLTs) in the airways of patients with EIB (15, 16), particularly the ratio of CysLTs to prostaglandin E_2 (PGE_2) (15). A recent study also found that patients with EIB relative to asthmatics without EIB have a reduction in the levels of the protective eicosanoid lipoxin A4 (23). The levels of 8-isoprostanes, non-enzymatic products of phospholipid oxidation, were increased in exhaled breath condensate (EBC) of asthmatics with EIB and correlated with the severity of EIB (24). As in prior studies (25) a recent study found that the fraction of exhaled nitric oxide (F_{ENO}) is elevated in asthmatics with EIB, and furthered the understanding of this relationship by showing that the relationship between F_{ENO} and EIB was restricted to subjects with atopy (26). Angiopoetin 2, a mediator that enhances microvascular permeability, is increased the airways in asthma and is correlated with the severity of EIB (27). Among children with asthma, including obese children, the severity of EIB was positively correlated with serum leptin and negatively with serum adiponectin (28). In addition, the levels of 25-hydroxy-vitamin D were reduced among subjects with asthma and were lower in asthmatics with EIB relative to those without EIB (29).

Inflammatory mediator release in the airways during EIB

Although the precise nature of the underlying stimulus for mediator release in the airways is not known with certainty, there is strong evidence that mediators from mast cells and eosinophils are released into the airways during EIB, and that this mediator release is the predominant cause of EIB (14, 30). During exercise, heat and water are transferred out of the airways to equilibrate the inspired air to the temperature and humidity of the lower airways. At the epithelial surface there is a transfer of water from the osmotically sensitive epithelial cells via the tight junctions, as well as a thermal gradient. Though osmotic stimuli are also known to directly activate inflammatory cells such as mast cells (31), it is reasonable to also consider that the stimulus of exercise or hyperpnea is predominant sensed by the airway epithelium leading to the activation of inflammatory mediator release from leukocytes residing in close contact to the epithelium. Two recent studies indicate that epithelial stress occurs during exercise *in vivo* by demonstrating that clara cell secretory protein (CC16) measured in the urine following challenge is increased after exercise and isocapnic hyperpnea challenge (32, 33).

The non-invasive method of exhaled breath condensate (EBC) has been used recently to better understand the nature of mediator release in the airways following exercise challenge. The levels of CysLTs in EBC were higher in the asthma group with EIB and increased after exercise challenge most notably in the EIB positive group; further, the change in CysLTs in EBC following challenge was correlated with the severity of EIB (34). These findings are consistent with the findings identified in induced sputum demonstrating a sustained increase

in CysLTs and other bronchoconstrictive eicosanoids such as PGD_2 in the airways following exercise challenge to induce EIB (14, 30). Mast cells and eosinophils are strongly implicated as the cellular sources of CysLTs and other eicosanoids in EIB. The eosinophil product eosinophilic cationic protein (ECP) is released into the airways following exercise challenge in patients with EIB (14). Mast cell degranulation occurs during exercise challenge as evidenced by histamine and tryptase release into the airways following challenge (30).

The connection between inflammatory eicosanoid release by leukocytes and epithelial stress is not initially obvious, since the epithelium itself is thought to have relatively limited capacity to synthesize CysLTs. The epithelium may directly lead to eicosanoid release through 15-lipoxygenase-1 (15-LO-1) since the levels of the 15-LO product 15*S*-hydroxyeicosatetranoic acid (15*S*-HETE) are increased after exercise challenge in subjects with EIB (35). The epithelium is also a major source of PGE_2 that is known to inhibit EIB when given by inhalation. The production of PGE_2 actually decreases post exercise challenge among asthmatics with EIB (30), and the ratio of CysLTs to PGE_2 increases in asthmatics post challenge, while there is a decrease in this ratio in normal subjects (35) (Figure 1). A unifying explanation for these findings is that the epithelium serves as a key regulator of the balance of eicosanoids in the airways by activating the release of bronchoconstrictive eicosanoids in inflammatory cells in close contact and by alterations that reduce the synthesis of PGE_2. The epithelium has reduced *in vitro* capacity for PGE_2 synthesis when treated with IL-13 through a reduction in the synthetic enzymes cyclooxygenase-2 (COX-2) and PGE synthase 1 (36).

Recent provocative data from a single research group contradicts older studies that have generally failed to demonstrate a cellular influx into the airways following exercise challenge (37, 38), or an increase in airway hyperresponsiveness (39, 40). An increase in high sensitivity C-reactive protein (CRP) was identified only in asthmatics with EIB following exercise challenge (41). In addition, the F_{ENO}, serum ECP and AHR to inhaled histamine were all increased following exercise challenge in asthmatics with EIB (41). Further they found that RANTES and eotaxin were increased in EBC in asthmatics relative to controls, and that the levels of RANTES and eotaxin were increased in EBC after exercise challenge only in the group with EIB, but not in asthmatics without EIB (42, 43). These are provocative findings that require further confirmation, but suggest that exercise challenge may trigger chemokines involved in leukocyte recruitment and AHR in subjects that are susceptible to this disorder.

Regulation of eicosanoid synthesis by secreted phospholipase A_2 ($sPLA_2$)

The first rate-limiting step in the formation of the CysLTs and other eicosanoids is the release of arachidonic acid from membrane phospholipids that is regulated by the PLA_2 enzymes. In addition to the cytosolic $PLA_2\alpha$ ($cPLA_2\alpha$), several secreted PLA_2s ($sPLA_2$)s have been implicated in eicosanoid synthesis, and may preferentially direct eicosanoid production toward LT synthesis. In humans, increased $sPLA_2$ activity has been identified in nasal lavage fluid and in bronchoalveolar lavage (BAL) fluid following allergen challenge, but the identities of the $sPLA_2$s were not characterized. We characterized $sPLA_2$ gene expression in induced sputum cells of asthmatics with EIB, and found significant expression of $sPLA_2$ group II, X and IIA enzymes (35). In a subsequent study examining the identities of $sPLA_2$s in BAL fluid of asthmatic and non-asthmatic subjects, the $sPLA_2$ groups IIA and X predominated, but only $sPLA_2$-X was elevated in association with lung function and eicosanoid formation in the airways (44) (Figure 2). It is notable that $sPLA_2$-X is expressed predominantly in the airway epithelium (44) as we recently found that transglutaminase 2 (TGM2) is increase in the airways of patients with EIB and serves as a regulator of $sPLA_2$-X activity (18) (Figure 3). Since $sPLA_2$-X is secreted and can act on other target cells such as

eosinophils to initiate eicosanoid formation, we examined the effects of exogenous $sPLA_2$-X on human eosinophils and found that $sPLA_2$-X rapidly initiated CysLT formation in eosinophils in a manner that was dependent upon the enzymatic activity of the enzyme, but occurred via activation of p38 and c-Jun MAPK (JNK) and $cPLA_2\alpha$ (45). *In vivo*, genetic deficiency of either $sPLA_2$-V or $sPLA_2$-X in a murine model of asthma attenuates the development of allergen-induced inflammation, mucus release, and AHR (46, 47), as does inhibition of human $sPLA_2$-X that was inserted under the endogenous promoter in a mouse model (48). These findings suggest that $sPLA_2$-X may serve as a key regulator of eicosanoid formation in the airways and that this enzyme is strongly implicated in features of AHR such as EIB.

Sensory nerve involvement in EIB

An important study using isolated capsaicin-sensitive neurons demonstrated that these neurons respond directly to the CysLT LTD_4 via the $CysLT_1$ receptor, and increased the excitability of these neurons to other electrical and chemical stimuli (49). This study is important because two studies conducted in animal models of EIB indicate that the mechanism of bronchoconstriction is mediated through the sensory nerve activation with retrograde axonal transmission via the release of neurokinins (50, 51). These data are also consistent with our findings in humans that goblet cell mucin 5AC (MUC5AC) is released into the airways during EIB in association with the levels of CysLTs and neurokinin A (NKA) suggesting that CysLTs mediate the activation of sensory nerves and mucus release during EIB in humans (52).

Conclusions

Recent studies have advanced our understanding of EIB as a distinct syndrome in asthma that is related to indirect AHR, and is notable for increased production of CysLTs and shedding of epithelial cells into the airway lumen (Figure 4). Exercise challenge serves as a stimulus to the airway epithelium and adjacent leukocytes resulting in sustained CysLT and PGD_2 release in association with smooth muscle contraction and the release of MUC5AC that may be the consequence of sensory nerve activation. Several lines of evidence indicate that mast cells and eosinophils serve as the principal sources of inflammatory eicosanoids in this disorder. Recent work has identified the strong expression of $sPLA_2$-X in the airway epithelium and elevated levels of $sPLA_2$-X protein in BAL fluid of patients with asthma. A genome-wide expression study identified TGM2 with increased expression in asthma and that found TGM2 serves as a regulator of $sPLA_2$-X. The $sPLA_2$-X enzyme acts on target cells such as eosinophils to initiate cellular eicosanoid synthesis. These studies suggest that the airway epithelium serves as an important regulator of the production of inflammatory eicosanoids by leukocytes.

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Abbreviations

15-LO-1 15-Lipoxygenase-1

15*S*-HETE	15*S*-Hydroxyeicosatetranoic Acid
AHR	Airway Hyperresponsiveness
BAL	Bronchoalveolar Lavage
COX-2	Cyclooxygenase-2
CPA3	Carboxypeptidase A3
CRP	C-reactive protein
cPLA$_2$α	Cytosolic Phospholipase A$_2$α
CysLT	Cysteinyl Leukotrienes
EBC	Exhaled breath condensate
ECP	Eosinophilic Cationic Protein
EIB	Exercise-induced Bronchoconstriction
F$_{ENO}$	Fraction of Exhaled Nitric Oxide
JNK	c-Jun MAPK
ICS	Inhaled Corticosteroid
IL-13	Interleukin-13
LT	Leukotriene
LTRA	Leukotriene receptor antagonist
MUC5AC	Mucin 5AC
PG	Prostaglandin
Q	Perfusion
sPLA$_2$	Secreted Phospholipase A$_2$
TGM2	Transglutaminase 2
Va	Alveolar ventilation

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Key Points

1. Exercise-induced bronchoconstriction (EIB) is an asthma phenotype with epithelial shedding and increased production of inflammatory mediators such as leukotrienes.
2. EIB in childhood is a risk factor for persistent asthma in adulthood.
3. Following exercise challenge, mediators are released into the airways from mast cells and eosinophils.
4. A regulator of leukotriene formation call secreted phospholipase A_2 group X ($sPLA_2$-X) has been identified in the airways of patients with asthma.
5. Transglutaminase 2 is overexpressed in the epithelium of patients with asthma and serves as a regulator of $sPLA_2$-X activity.

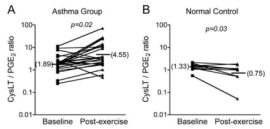

Figure 1.

Opposing effects of exercise challenge on the CysLT to PGE_2 ratio in induced sputum. Asthmatics with EIB have an increase in the CysLT to PGE_2 ratio in response to exercise (A), while normal controls have a decrease in the CysLT to PGE_2 ratio following exercise challenge (B). Adapted from reference 30.

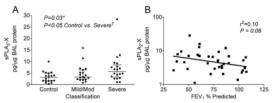

Figure 2.

Levels of $sPLA_2$-X protein in BAL fluid in relation to asthma severity and lung function. The levels of $sPLA_2$-X in BAL fluid normalized to total protein were higher in asthmatics relative to controls, with the largest difference in the severe asthma group relative to controls (A). The figure shows the medians and interquartile ranges. The levels of $sPLA_2$-X were associated with lung function among asthmatics by regression analysis (B). Adapted from reference 44.

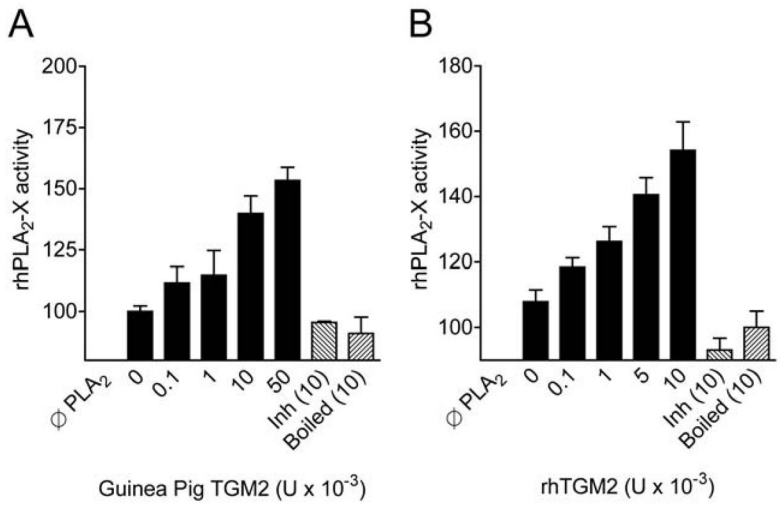

Figure 3.

Increase in sPLA2-X enzyme activity mediated by TGM2. Pre-incubation of recombinant human $sPLA_2$-X with purified TGM2 from guinea pig liver (A) or with recombinant human TGM2 (B) causes an increase in the PLA_2 activity of the $sPLA_2$-X enzyme. Denaturing the TGM2 with heat (boiled) or inhibiting the activity of the enzyme by saturating the enzyme with N-carbobenzoxy-Gln-Gly (Inh) demonstrate that the *in vitro* findings are due to the enzymatic activity of TGM2. Adapted from reference 18.

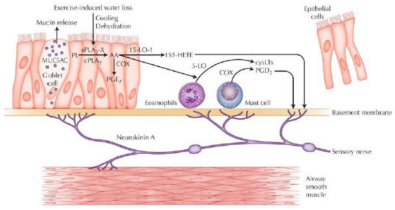

Figure 4.

Disease model of exercise-induced bronchoconstriction (EIB) pathogenesis. Asthmatics with EIB have increased concentrations of shed epithelial cells, CysLTs, and CysLT/PGE_2 ratio in induced sputum. Exercise challenge initiates the production of CysLTs, PGD_2, and 15*S*-HETE, and a reduction in PGE_2. The release of $sPLA_2$-X by the airway epithelium may initiate CysLT production in adjacent leukocytes. Contraction of the airway smooth muscle and mucin release occurs in part through retrograde axonal transmission in sensory nerves that release neurokinin A. 15-LO-1 - 15-lipoxygenase-1; 5-LO - 5-lipoxygenase; COX - cyclooxygenase; cPLA2 - cytosolic phospholipase A2; MUC5AC - mucin 5AC; PL - phospholipids. Adapted from reference 53.