Etiology of Exercise-induced Asthma: Physical Stress-induced Transcription

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Current Allergy and Asthma Reports 2007, **7:**27–32
Current Science Inc. ISSN 1529-7322

Exercise-induced asthma (EIA) occurs with a high prevalence in both asthmatic and nonasthmatic individuals. Although understanding of the functional genomics (proteomics) in sports medicine remains limited, this review focuses on immunologic changes as reflected in transcriptional regulation in respect to EIA. Studies demonstrated that leukotrienes play a significant role in EIA. Exercise increases the distribution of leukotrienes and influences the leukotriene transcription pathway; it could be shown that the genes *ALOX5* and *ALOX5AP* encoding for 5-lipooxygenase (5-LO) and 5-lipoxygenase–activating protein (FLAP) as well as activators for 5-LO, p38 mitogen-activated protein kinase (MAPK), and others, are enhanced after exercise in healthy subjects. Possibly EIA is triggered via leukotriene release if a predisposition or other conditions (eg, epithelial injury and repair) are present. Furthermore, exercise influences transcription factors such as nuclear factor-kappa B (NF-κB), activator protein-1 (AP1), cytokines, and chemokines and promotes cellular responses linked to EIA, which are possibly able to modify further the incidence or the severity of EIA.

Introduction

Exercise-induced asthma (EIA) has a high prevalence not only in patients with asthma but also in individuals without any symptoms after physical activity [1••]. As shown in the literature, the prevalence ranges from 10% to 50% in elite athletes; moreover, in 9% to 12% of school-age children, exercise-induced bronchospasm or EIA occurs during or more commonly after exercise [2,3]. Two different terms and definitions are used: exercise-induced bronchoconstriction (EIB; bronchial obstruction and spasm brought on by exercise in subjects with normal lung function at rest) and exercise-induced asthma (the exacerbation of a patient's asthma during and after exercise). Sometimes both terms are used interchangeably [3]. In this review EIA is used strictly for both situations, as suggested by Storms [3]. A reduction in forced expiratory volume in 1 second (FEV_1) of more than 10% from the pre-exercise value is usually required for the diagnosis of EIA [4••]. The precise mechanisms giving rise to EIA are still debated, a situation that most likely will continue for the near future.

However, Anderson and Kippelen [4••] have published an excellent flow chart describing the acute situation and progression in exercise-induced asthma. It describes the provoking stimulus of water loss from the humidifying inspired air (eg, by evaporative water loss), and presents how this primary effect results in two downstream mechanisms—airway cooling on the bronchial vasculature with vasoconstriction and reactive hyperemia, or increase of the osmolarity of the airway surface liquid, or both—leading to an activation of cellular defense mechanisms that includes the release of different mediators. These effects are possibly accompanied by epithelial injury in response to dehydration of the airway surface, as described by Anderson [5], and the repair process may increase bronchial responsiveness to exercise-induced mediators. However, the predominant cause of EIA has not yet been determined. These effects are not preconditions of EIA only in asthmatic individuals; they also occur in healthy and asymptomatic persons. Thus it is necessary to shed more light on the immunologic changes in EIA. Many authors agree that different inflammatory mediators have definitive effects on the pathogenesis of EIA.

This review describes the effects of transcription response to exercise with a specific focus on the leukotriene (LT) pathway, by which bronchoconstriction is triggered when a predisposition is present. However, in this new field of functional genomics (proteomics) sports medicine, only a few studies deal specifically with exercise-induced transcriptional response in genes that are relevant to asthma. The interested reader should realize that some of the data presented here have been collected from in vitro experiments, animal studies, or healthy nonasthmatic individuals. The evidence for their role in EIA in humans remains to be proven.

Physical Stress and Leukotrienes

Although there is no definitive evidence that EIA has central inflammatory routes, investigations in animal models demonstrated that dry air hyperpnea increases airway osmolarity [6] and results in a release of epithelial cells and eicosanoids into the airways [7,8]. These experiments seem to indicate an inflammatory mechanism, but other investigators have failed to demonstrate the release of mast cell mediators and eicosanoids into the airways in humans following exercise [9,10]. However, these studies possibly failed to collect relevant airway material because it was obtained from the distal part of the airway system [1••]. Hallstrand et al. [1••] extracted sputum from the conduction airways and found that mast cell mediators such as histamine and tryptase as well as cysteinyl (cys) LTs, products of mast cells and other airway cells, are generated during EIA. Several studies have shown increased levels of cys-LTs in the urine of subjects with EIA after exercise challenge, although this was not observed in all studies [11–13].

However, other studies confirmed the role of LTs in EIA. Different studies depict the efficiency of receptor antagonists against the cys-LTs or inhibition of 5-lipoxygenase (5-LO) in EIA with a significant reduction of the decrease in FEV_1 [12,14,15]. In a double blind, placebo-controlled study with montelukast, a leukotriene receptor antagonist, taken 20 to 24 hours before exercise, significant protection against EIA was observed in patients with mild asthma over the 12 weeks of the study [14]. Dahlen et al. confirmed the beneficial effects of a leukotriene receptor antagonist in EIA [16]. Montelukast also seems to be able to inhibit 5-lipooxygenase (5-LO), a central enzyme in the LT pathway [1]. As demonstrated in different studies, acute exercise increases the LT concentration in blood; however, less is known about the molecular mechanisms by which exercise enhances LT concentrations [17].

The first step in LT biosynthesis is the activation of phospholipase A_2 (PLA_2), which then hydrolyzes membrane phospholipids to release arachidonic acid (AA). This step requires calcium and is ATP-dependent. AA will be further metabolized by 5-LO to leukotriene (LT) A_4 but this step depends on the interaction of 5-LO with a nuclear membrane protein, 5-lipoxygenase–activating protein (FLAP). LTA_4 will be converted to either LTB_4 by the LTA_4 hydrolase or conjugated with glutathione by LTC_4 synthase to cys-LTs [18]. Leukotriene biosynthesis occurs mainly in granulocytes, monocytes or macrophages, and mast cells, whereas LTB_4 is mainly produced in neutrophils and monocytes and LTC_4 in eosinophils, basophils, and mast cells [19]. Both 5-LO and FLAP are essential for the biosynthesis of LTs, and it appears that both are regulated at the transcriptional level and that mRNA increases after cell activation.

Increased expression of 5-LO and FLAP has been described in peripheral blood leukocytes in asthmatic subjects, and enhanced levels of FLAP have been found in blood eosinophils in allergic asthmatic patients, together with a diminished response to interleukin (IL)-5, suggesting an in vivo exposure of endogenous IL-5 [20,21]. It was shown in a first study that physical activity is able to trigger transcription of *ALOX5* and *ALOX5AP* coding for 5-LO and FLAP in healthy subjects (Fig. 1) [22•]. In this study a laboratory exercise test with an exercise intensity of 90% of the individual anaerobic threshold over 90 minutes was carried out to examine stress-induced changes in gene expression with a special focus on EIA-related genes.

Of particular interest, using microarray analysis it was found that the transcription of *ALOX5* as well as *ALOX5AP* was enhanced after this type of exercise [22•]. At present it remains unclear if regulation differs in healthy and asthmatic subjects. Furthermore, the influence of existing polymorphisms (eg, in *ALOX5*) has not been evaluated until now. Without the results of these investigations, it is impossible to fully appreciate the role of exercise-induced increase in the transcriptions encoding 5-LO and FLAP in the development of EIA.

However, exercise not only is able to increase the mass of 5-LO or FLAP but also can influence the 5-LO activity via changes in the p38 mitogen-activated protein kinase (MAPK) pathway (Fig. 1). Protein phosphorylation is the predominant normal regulatory mechanism for the transduction of extracellular signals leading to the activation and redistribution of enzymes and transcription factors. It was shown that p38 MAPK-regulated mitogen-activated protein kinase-activated protein (MAPKAP) kinase-2 and MAPKAP kinase-3 from stimulated leukocytes can phosphorylate 5-LO in vitro [19]. The p38 MAPKs are activated by different inflammatory stimuli, chemotactic factors, phorbol esters, and Ca^{2+} mobilizing agents, as well as by cellular stress factors such as osmotic shock, ultraviolet light, and heat shock.

Physical activity such as exercise training also has the ability to increase the p38 MAPK and protein as well as the protein for signal transducer and activator of transcription (STAT) 3, corresponding to the increase of these mRNAs as shown by microarray analysis in an animal model [23]. In human subjects p38 MAPK can be phosphorylated in skeletal muscle in response to cycling and marathon running [24]. P38 MAPK is also enhanced in human leukocytes after endurance exercise (Hilberg, Unpublished data), and it was shown that low muscle glycogen results in phosphorylation of nuclear p38 MAPK [25]. Activation of the pathway for the extracellular signal-regulated kinases 1 and 2 (ERK1/2)—members of the MAPK family—has also been reported in human skeletal muscle after acute cycling exercise and marathon running (Fig. 1) [24].

The MAPK signaling cascade can be divided into diverse pathways mediated via ERK1/2, p38 MAPK, and c-Jun NH2-terminal kinases (JNK) [26]. The p38α/MAPKAP kinase-2 pathway is crucial to the production

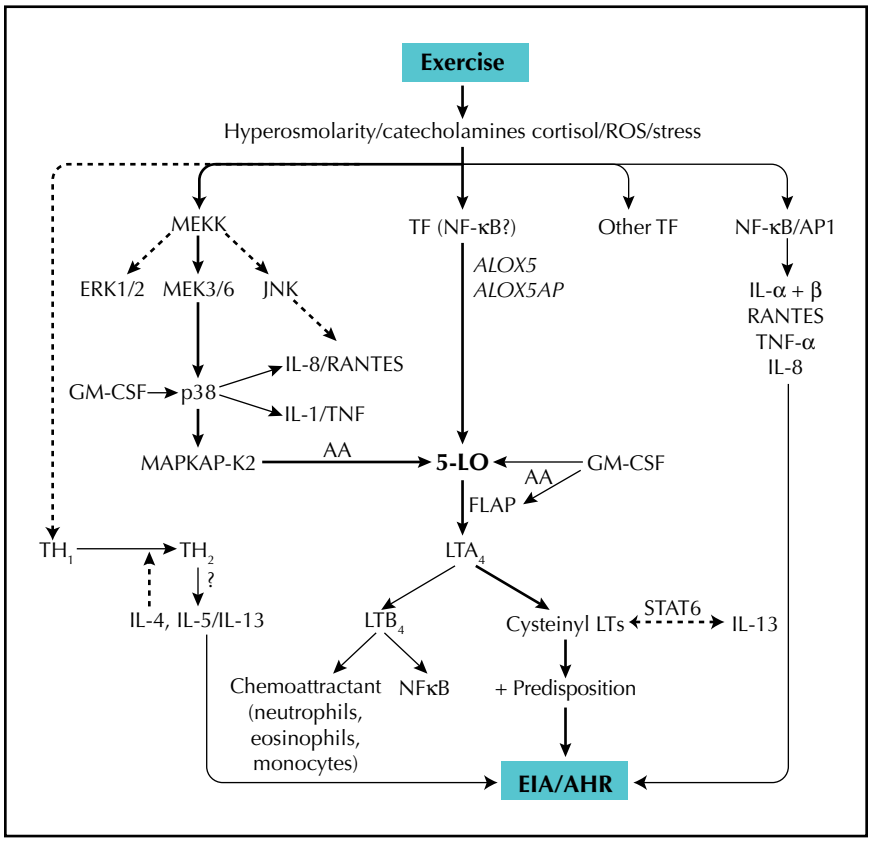

Figure 1. A model of transcription response and activation changes in exercise-induced asthma (EIA)–relevant mediators focusing on the leukotriene pathway. AA—arachidonic acid; AHR—airway hyperresponsiveness; AP-1—activator protein-1; cys-LTs—cysteinyl leukotrienes; ERK—extracellular signal-regulated kinase; FLAP—5-lipoxygenase–activating protein; GM-CSF—granulocyte-macrophage colony-stimulating factor; IL—interleukin; JNK—c-Jun NH2-terminal kinases; LT—leukotriene; LTA_4—leukotriene A_4; LTB_4—leukotriene B_4; MAPKAP—mitogen-activated protein kinase-activated protein; MEKK—MAPK/ERK kinase; MEK—MAPK/ERK; NF-κB—nuclear factor-kappa B; RANTES—regulated on activation, normal T expressed and secreted; ROS—reactive oxygen species; STAT6—signal transducer and activator of transcription; TF—transcription factor; T_H1—T-helper 1; T_H2—T-helper 2; TNF—tumor necrosis factor. *Bold arrow*—central pathway, *dotted arrow*—side pathway.

of inflammatory cytokines and signaling; in addition, p38α MAPK phosphorylates a variety of transcriptional activators regulating expression of genes encoding inflammatory cytokines [27]. However, the situation after exercise is more complex because the p38 MAPK signal transduction can be mediated by four isoforms (α,β,δ,γ) with different specificities and different regulation [26]. Nevertheless, inhibitors of p38 MAPK have been shown to block the production of IL-1, tumor necrosis factor (TNF), and other cytokines [28].

Although these facts have been investigated in different studies, the direct relationship between the exercise-induced changes in MAPK, 5-LO, and LTs on the one hand and the symptomatic dimension of EIA on the other has not been described in detail until now. Furthermore, it was shown that prostaglandin E_2 (PGE_2) is decreased in the induced sputum after exercise [1], and exercise and training status influences the gene expression coding for the prostaglandin endoperoxide synthase 1 (PTGS1) (Hilberg, Unpublished data). A change in the balance between cys-LTs and PGE_2 can favor bronchoconstriction in the period after exercise [1].

Physical Stress and Transcription Factors

Transcription factors (TF) represent a family of proteins that can bind to regular sequences, usually in the 5′ upstream promoter region of target genes, and increase or possibly decrease the rate of gene transcription [29]. Nuclear factor-kappa B (NF-κB) plays a significant role in the regulation of cell activity [30]. Five members of the NF-κB family exist, with p50, p52, p65 (RelA), c-Rel, and RelB forming several homo- and heterodimers, the most common active form of which is the p50/RelA or p52/RelA heterodimer. Formation of the different dimers of NF-κB subunits accompanies the different DNA-binding specificities and transactivation potential [31].

Different studies demonstrated that exercise activates NF-κB. Ji et al. [32] studied the effects of physical exercise on NF-κB in rat skeletal muscle and demonstrated that exercised rats showed higher levels of NF-κB binding and p50 protein content in the muscle. Vider et al. [33] showed that physical exercise with 80% maximal oxygen consumption over 1 hour may trigger NF-κB activation in peripheral blood lymphocytes of physically fit young men.

Another study investigated NF-κB in peripheral blood mononuclear cells of 12 healthy young men after a 1-hour run on a treadmill at a velocity corresponding to the anaerobic threshold [34]. The authors demonstrated that exercise leads to increased NF-κB (p50/p65) binding activity to a NF-κB consensus sequence in nuclear extracts of peripheral blood mononuclear cells [34]. Increased NF-κB activity has been observed in the key locations in the airways of asthmatic patients as well as in animal models of asthma [31].

In the opinion of Popescu [35], NF-κB inhibition represents a key strategy in asthma treatment because of the potent anti-inflammatory effects of these inhibitors. NF-κB regulates a comprehensive number of gene-

encoding cytokines (eg, IL-1α and β, IL-2, IL-6, IL-8, IL-9, IL-10–13, and IL-15), chemokines (eg, RANTES [regulated on activation, normal T-cell expressed and secreted]), growth factors, and other immunoregulatory molecules, which are listed in an excellent review by Kumar et al. [31]. Although the facts point to the relevance of NF-κB in the development of asthma and show that NF-κB is enhanced after acute exercise, the exact role of NF-κB and the exercise-induced rise of NF-κB in the process of EIA remain unclear (Fig. 1).

Activator protein-1 (AP1) is another transcription factor closely related to asthma. A large number of asthma-relevant genes (eg, those encoding the prototypic T-helper [T_H] 2 cytokines IL-4, IL-5, and IL-13) are overexpressed in asthma and most of them contain binding sites for NF-κB, AP1, or both within their promoter or enhancer and are therefore believed to be dependent on NF-κB, AP1, or both for their expression [36].

Desmet et al. [36] showed that specific AP-1 inhibition in the airways may offer therapeutic options in the control of established asthma. Hollander et al. [37] demonstrated that AP-1 binding is enhanced in rat muscle after exercise. However, changes in AP-1 after exercise in relationship to EIA have not been tested.

Many other transcription factors exist that are modified in asthmatic subjects and are influenced by exercise, such as the glucocorticoid receptor and nuclear factor of activated T-cells (NFAT) [29,35], which have direct relationships to NF-κB, AP-1, or STATs. However, a link between the various exercise-induced changes has not been revealed to date.

Physical Stress, Cytokines, and Chemokines

Different cytokines and chemokines are involved in the pathogenesis of asthma. Particularly important in the pathogenesis of asthma are T_H2 cytokines (eg, IL-4, IL-5, and IL-13). A central function of IL-4 is to promote the differentiation of T_H2 cells, which are involved in the allergic response [38]. Bronchial biopsy studies have shown an increased expression of IL-4 at mRNA and protein level in the airway mucosa of people with atopic and even nonatopic asthma in comparison with nonasthmatic controls [39].

IL-5 is an essential cytokine in the eosinophilic inflammation of asthma [38]. The blockade of IL-5 inhibits eosinophilic inflammation and airway hyperresponsiveness in primate models of asthma [38]. As for IL-4, an enhanced expression of IL-13 mRNA and protein has been detected in the airways of people with asthma [39].

Many studies point to IL-13 as a key effector cytokine in asthma, but the specific targets of IL-13 are unclear [40]. The effects of IL-13 (eg, increased airway responsiveness, mucus hypersecretion) are mediated by its binding to a heteromeric receptor made up of IL-4Rα and either IL-13Rα1 or IL-13Rα2 [41].

Chavez et al. [41] showed that a close relationship exists between LTC_4 and IL-13 because these are dependent on or signal through STAT6 to increase airway responsiveness and both agonists regulate the expression of each other's receptor (Fig. 1). An increase in STAT6 in leukocytes after exercise has been shown in one study [22•]. Strenuous and particularly long-lasting exercise influences a whole orchestra of inflammatory (eg, IL-1β, TNF-α, IL-8) and anti-inflammatory (eg, IL-6, IL-10, IL-1ra) cytokines [42]. For example, TNF-α is known for inducing responsiveness in vitro and in vivo [4]. Catecholamines and cortisol, which are known to increase under strenuous and (particularly cortisol) after long-lasting exercise, provoke a shift in the human type-1 and type-2 cytokine balance toward a type-2 response (Fig. 1) [43].

Although exhaustive exercise seemed to induce a late IL-4 response with an increase 2 hours after maximal exercise [43], changes in these asthmatic-relevant cytokines are small. Suzuki et al. [43] and Peake et al. [44] found no enhanced IL-5 levels after a marathon race and no increase in plasma concentration of IL-5 and IL-13 after a high-intensity trial on a treadmill for 60 minutes.

Tahan et al. [45] studied the role of chemokines such as RANTES, eotaxin, thymus and activation-regulated chemokine (TARC), and others on exercise-induced bronchoconstriction and found that exercise does not cause any changes in the systemic levels or transcription of eosinophilic chemokines. However, a close relationship between MAPK and RANTES exists, because it was shown that p38 MAPK and JNK pathways regulate hyperosmolarity-induced IL-8 and RANTES production by bronchial epithelial cells [46]. In addition, the hyperosmolarity-, cooling and rewarming–induced increase in RANTES and IL-8 can be attenuated by inhaled corticosteroids, but this does not depend on p38 MAPK and JNK [47].

Physical Stress and Histamine

Histamine as a mediator in the granules of mast cells has been judged to be an important mediator in EIA. It appears that the role of histamine has been somewhat overrated in EIA because histamine antagonists have failed to show the ability to distinctly and consistently reduce EIA. However, it has been shown that loratadine has beneficial effects in more severe cases of EIA [13,16]. Apparently, histamine seems to become more important when the exercise stimulus is more intense. Strenuous exercise increases plasma and total histamine, but this is dependent on training status and possibly IL-8 and IL-1β release [48].

Physical Stress and Eosinophils, Neutrophils, and Mast Cells

The eosinophils are known as central effector cells in the inflamed asthmatic airway. They are important because of their ability to release toxic basic proteins and lipid

mediators such as cys-LTs or cytokines and chemokines such as IL-5, eotaxin, or RANTES. However, the results of different studies show the role of the neutrophils in airway obstruction via the release of lipid mediators, reactive oxygen intermediates, and elastase, which leads to obstruction, epithelial damage, and remodeling.

Exercise leads to an increase of neutrophils and eosinophils in peripheral blood; furthermore, the exercise-induced increase in LTB_4, IL-8, and TNF-α together with the granulocyte-macrophage colony-stimulating factor (GM-CSF) enhanced the chemoattraction of neutrophils and reduced apoptosis [49]. The GM-CSF mRNA seems to be moderately increased after exercise (Hilberg, Unpublished data).

The neutrophils also produce several mediators including lipids (LTB_4, platelet-activating factor [PAF], thromboxane A_2 [TXA2], LTA_4), proteases (elastase, collagenase MMP-9), and cytokines. Neutrophils generate not only the precursor LTA_4 but also large amounts of LTB_4, which is a potent chemoattractant for neutrophils, eosinophils, monocytes, and fibroblasts. In addition LTB_4 activates NF-κB and supports the synthesis of IL-5, IL-6, and IL-8 and enhances immunoglobulin E (IgE) synthesis in B cells [49]. In vitro priming of human neutrophils and monocytes by GM-CSF of IL-3 may involve cytosolic phospholipase A2 (cPLA2) activation, leading to an increase in arachidonate availability, followed by gene transcription and protein synthesis of 5-LO and FLAP (Fig. 1) [21]. It was shown that treatment of neutrophils with GM-CSF for 30 minutes increased 5-LO and FLAP protein synthesis [19]. In addition GM-CSF is an activator of the p38 MAPK pathway [19].

Mast cells are known to be important as mediator-secreting cells in asthma. Cross linkage of IgE on mast cells results in the rapid release of different mediators as well as the sustained synthesis and release of cytokines, chemokines, and growth factors [50]. TNF-α released by activated mast cells not only induces a molecule adhesion cascade that is responsible for neutrophil and eosinophil recruitment during the late asthmatic response to allergens but also stimulates, in an autocrine manner via the TNF-α-receptor 1, a mediator release by activation of NF-κB [50]. In EIA the mast cells become activated for mediator secretion as shown by an increased excretion of urinary metabolites of prostaglandin D_2 and cys-LTs. The exercise or hyperosmolar challenge causes a direct or indirect bronchoconstrictor response linked to the release of cys-LTs, prostanoids, and histamine or other mediators together with epithelial injury and repair processes or other preconditions [50].

Conclusions

The pathogenesis of EIA is complex; it may be induced by an increase of osmolarity, as well as cooling and reactive hyperemia in the airways, but it also involves exercise-induced immunologic changes at the transcriptional level, specifically in the leukotriene transcription pathway. It was shown that the genes encoding for 5-LO and FLAP as well as activators for 5-LO (eg, p38 MAPK) are enhanced after exercise in healthy individuals, and are possibly able to trigger EIA via leukotriene release if a predisposition is present.

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