The evidence of exercise-induced bronchoconstriction in endurance runners; genetic basis and gender differences

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Exercise is one of the most common triggers of bronchospasm in persons with and without chronic asthma. Exercise-induced bronchoconstriction (EIB) is defined as transient, reversible bronchoconstriction that develops after strenuous exercise (23). It is a heterogeneous syndrome occurring in a variety of settings, ranging from the asymptomatic military recruit (whose condition is detected by diagnostic exercise challenge) to the leisure-time athlete with known asthma to the elite athlete for whom EIB may represent an overuse or injury syndrome. If exercise is the only identified trigger for bronchoconstriction, it is called EIB. However, when it is associated with known asthma, then it is defined as EIB with asthma. It is unclear if EIB in those with and without chronic asthma results from the same mechanism. One of the new approaches for evaluating of the pathogenesis of EIB or exercise-induced asthma is analysis of the cellular responses and cytokine production in the airways. When the natural mucosal warming and humidification processes are disturbed / overrun by exercise-associated hyperventilation, this results in changes in osmolarity which will then trigger the release of inflammatory mediators causing bronchospasm.

Furthermore, this cascade of events may be exacerbated by pre-existing airway inflammation and airway remodeling. Evidence suggests that histamine, leukotrienes and prostanoids are likely central mediators involved in this response. Recent studies continue to demonstrate heterogeneity in the airway inflammatory response to EIB, reporting correlations of bronchospasm with eosinophils and eosinophil cationic protein (ECP), lipoxin A4, phospholipase A2, and endothelin-1 (24).

With this letter, we like to draw the attention to some findings from our recent work which may have relevance for this question (EIB/EIA) but have not been discussed in an integrative, comprehensive fashion. One hour of high intensity aerobic exercise, corresponding to 93% VIAT (21), or a half-marathon (1) significantly induced the up-regulation of genes such as Prostaglandin D2 receptor (PTGDR), interleukin-18 receptor-1 (IL-18R1), interleukin-18 receptor accessory protein (IL-18RAP), β2-adernergic receptor (ADRB2), arachidonate 5-lipoxygenase (ALOX-5), Endothelin-1 (EDN1, in LPS-stimulated cultures), and Cysteinyl leukotriene receptor-1 in healthy athletes, with females in luteal phase having either more dramatic or more prolonged regulation than male athletes. These observations are in good agreement with studies which have shown that female mice (19, 3) and rats (5,6) are more susceptible to induction of allergy and asthma, due to female hormone-induced cytokine release. In addition, clinical studies also have shown an important role of female sexual hormones regulating airway inflammation and allergic reactions in asthmatic women (18, 27). In summary, these studies point out that female hormones can induce a switch of Th1 to Th2 response, increasing allergic airway inflammation, in addition to an increase in the production of pulmonary nitric oxide, a classical marker of airway inflammation and hyperresponsivenes in asthmatic individuals (9,17).While previous studies have clearly demonstrated the involvement of Cysteinyl Leukotrienes (CYS-LTs) and their receptors in the development of airflow obstruction and in the pathophysiology of EIB (10,11,15), the functions of PTGDR, IL-18RAP, IL-18R1, and EDN1 in exercise-induced bronchoconstriction and/or asthma have not been described elsewhere so far. Recent studies have clearly pointed to the role of these genes in the pathophysiology of asthma, especially their roles in airway inflammation and bronchial hyperresponsiveness (2,22). For example, PTGDR (D prostanoid receptor) which is a classic type of transmembrane receptor specific for PGD2 has been shown to play an important role in allergic inflammation of the airways and asthma (22). In addition, IL-18RAP and IL-18R1 genes, which are specific receptors for IL-18 have been identified as candidate genes associated with increased susceptibility to airway hyperresponsiveness, bronchopulmonary dysplasia, and asthma (4,7,25,29,31). Moreover, increased serum levels of soluble IL-18 receptor complex in patients with allergic asthma have also been shown (14). It has been suggested that the co-expression of IL-18R1 and IL-18RAP is required for the activation of NF-κB and MAPK8 (JNK) in response to IL-18. The induction of both signaling pathways results in secretion of cytokines, a number of which (IL-8, MCP-1/2/3, G-CSF, and IL-6) have been associated with bronchoconstriction and bronchopulmonary dysplasia (7). Furthermore, IL-18-driven asthmatic responses via NF-κB have been associated with increased Th2 differentiation and activation, leading to release of IL-4, IL-5 and IL-13 (16,20).

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The strong exercise induced up-regulation of EDN1 which occurred when cultures were co-stimulated with pathogen (low dose endotoxin/LPS) also deserves our attention. Endothelin-1 is a potent vasoconstrictor that is produced by vascular endothelial cells and has been shown to play an important role in the pathogenesis of atopic asthma, airway obstruction and exercise-induced bronchoconstriction (26,12). It seems that EDN1 is involved in the pathophysiology of atopic asthma through the induction of serum IgE (12). The serum concentration of IgE is a well-stablished marker for the evaluation of asthma and bronchoconstriction (28,32).

Besides these observations, genetic association studies have also revealed a positive linkage of the genetic polymorphisms in PTGDR, IL-18RAP, IL-18R1, ADRB2, END-1 and ALOX-5 with asthma phenotypes (4,7,8,13,22,25,30), suggesting that the strong up-regulation of these genes may have some roles in the pathophysiology of EIB or EIA.

These results can be considered from several perspectives. First, our synopsis shows that exercise can significantly induce mRNA expression of a row of asthma-related genes, for instance, PTGDR, IL-18R1, IL-18RAP, ADRB2, ALOX-5, EDN1 (1,21). Given the dynamic nature of gene expression and the given the fact that microarrays can only reflect single time points, more can be expected to come in the future. Second, many of those genes (e.g. PTGDR, IL-18RAP) were only changed significantly in female athletes who were in the luteal phase of their menstrual cycle. Such findings suggest that the women who exercise in their luteal phase might be more susceptible to exercise-induced bronchoconstriction (EIB). Here it should be noted that all our female athletes were on a normal menstrual cycle. Of course hormonal regulation can be disturbed by excessive exercise/hard training up to the degree of amenorrhea. Although this was not the case of our set of female athletes, we cannot exclude that exercise-induced hormonal changes below the ”amenorrhoeic threshold” were involved in the mechanisms underlying our findings. Hormonal values which were assessed before exercise were however in normal ranges corresponding the second half of menstruation.

Third, our observation concerning EDN1, underlines that exercise and effects of concomitant pathogens can cooperate in the induction of important asthma-related genes.

These results accentuate a need for careful consideration of the pulmonary functions of athletes when programming the exercise training. While the strong association of the mentioned genes with asthma and bronchoconstriction has been demonstrated very well, we have to note that, unfortunately, there was no parallel evaluation of the pulmonary functions (i.e. FEV1, VO2, maximal expiratory flow) of athletes in our studies, which should be addressed in further studies.

Future studies are needed to measure the symptoms of exercise-induced bronchoconstriction and correlate these symptoms with the changes in asthma-related genes following exercise program. Clinical measurements of exercise-induced bronchoconstriction will enable a more precise discussion of the association of prolonged, exhaustive exercise and exercise-induced bronchoconstriction. This letter may help to draw the attention of the exercise immunology community to this open question.

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