Are leukotrienes involved in causing bronchial hyperresponsiveness?

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It is now widely accepted that airways inflammation is a vital factor in the pathophysiology of asthma [1]. Poorly controlled airways inflammation is thought to lead to symptoms of asthma such as wheeze, shortness of breath and tight chest. Evidence from many studies indicates that one way in which airways inflammation manifests itself is by causing bronchial hyperresponsiveness (BHR) [2]. The link between airways inflammation and BHR is clearly complex. There are however many studies which when taken together show that agents which cause medium term worsening of asthma such as viral upper respiratory tract infections [3] and allergen exposure in a sensitized individual [4] lead to a deterioration in airways inflammation and an increase in BHR. Conversely, improved control of asthma occurring either spontaneously or as a result of treatment with inhaled corticosteroids leads to an improvement in asthma control, a decrease in inflammation and improvement in BHR [5]. Due to this effect, the results of studies assessing BHR in relation to any new drug which affects the inflammatory cascade in asthma, are always keenly awaited. Reported in this issue of the European Respiratory Journal, is a study on the effects of the 5-lipoxygenase inhibitor zileuton on BHR [6]. How does this study relate to our current understanding of the role, if any, of leukotrienes, in the pathogenesis of airways inflammation or BHR?

Numerous studies clearly indicate that leukotrienes are released into the airways during induced and spontaneously occurring asthma attacks. There are also many studies which show that leukotrienes are potent bronchoconstrictors of animal and human airways in vivo and in vitro. There is increasing evidence that leukotrienes can increase certain components of airways inflammation in vivo. In animal models, inhalation of cysteinyl leukotrienes leads to a persistent increase in airway eosinophilia for up to 4 weeks [7]. This eosinophilia can be blocked by a cysteinyl leukotriene receptor antagonist [7]. In asthmatic subjects inhalation of cysteinyl leukotrienes causes an increase in airways eosinophils measured either in bronchial biopsies [8] or from induced sputum [9]. In humans there is little evidence that leukotriene (LT)B4 is important is eosinophil recruitment [10]. The limited evidence available suggests that LT B4 may cause neutrophil migration but has no effect on eosinophils [11].

A number of studies have looked for evidence that inhalation of leukotrienes increases BHR. Two studies have failed to show any effect of LT B4 on BHR despite giving doses which altered peripheral blood neutrophil levels [11, 12]. The evidence available on the effect of cysteinyl leukotrienes is equivocal. Some studies have shown that cysteinyl leukotrienes have an effect on BHR, whereas others have shown no effect. In general it has proved difficult to demonstrate an increase in BHR following leukotriene inhalation in normal subjects [13–15], although Bateman et al. [16] have shown an alteration in the plateau of the methacholine dose-response curve following inhalation of LTD4, and two studies have shown LTD4 causing an increase in BHR in normal subjects [17, 18]. In asthmatic subjects, inhalation of cysteinyl leukotrienes has in a number of studies been shown to increase BHR [19, 20]. It is tempting to speculate that the difference between the normal and asthmatic subject is due to leukotrienes causing an increase in eosinophil recruitment to the airways in the asthmatic subject, which they are unable to cause in the normal subjects, who have a lower number of circulating eosinophils. Studies in which agents are inhaled and an increase in BHR is sought are always methodologically difficult and with a number of putative asthmatic mediators it has proved difficult to obtain reproducible results. The vital question is whether drugs that act against the leukotriene pathway affect either components of airways inflammation or BHR.

There are preliminary reports that the cysteinyl leukotriene antagonist zafirlukast can decrease airways inflammation after segmental allergen challenge [21, 22] and that the leukotriene receptor antagonist montelukast can decrease circulating peripheral blood eosinophil levels [23]. A beneficial effect on sputum eosinophilia in chronic asthma has been reported in one study on the antagonist montelukast [24]. The 5-lipoxygenase inhibitor zileuton has been shown to have beneficial effects on airways and peripheral blood eosinophilia in nocturnal asthma though the number of subjects studied was limited [25]. A trial of a specific LT B4 receptor antagonist in allergen challenge caused a decrease in the number of neutrophils migrating into the airway, without having any effect on eosinophil numbers or the magnitude of the late asthmatic response [26]. This suggests that effects seen with a 5-lipoxygenase inhibitor are due to effects on cysteinyl leukotrienes rather than LT B4.

What of studies which have specifically investigated BHR? One study showed an attenuation of the increase in BHR occurring after a later response to allergen, however, BHR was measured at 6 h after allergen challenge rather than as is more conventional 24 h after challenge [27]. It has been suggested that the effect observed was due to a difference in airways function between the active and...
placebo group at the time BHR was measured [28]. A clinical study of zileuton showed that after cessation of chronic therapy an effect on cold air-induced bronchoconstriction was seen which persisted after zileuton was no longer likely to have been present in the blood [29]. Fischer et al. [29] suggested that this was due to a persist-ent beneficial effect on BHR rather than an immediate blocking effect on exercise. However this study was conducted on a very limited number of subjects, the time after cessation of drug when the cold air challenge was performed was variable and this was not the main outcome measure of the study [29]. One study with pranlukast (ONO1078) showed a small beneficial effect on BHR [30].

Few other studies have been reported which make the results of the study by Dekhuijzen et al. [6] of particular interest. As would be anticipated from studies of the effect of antileukotriene drugs on exercise [31] and cold air [32] a marked effect on the indirect challenge of nebulized distilled water was observed. The surprising result was that a single dose of zileuton caused a large improvement in BHR to histamine with a 2.1 doubling dose shift compared to placebo. The magnitude of the change is what one might associate with a functional antagonist which zileuton is not, or after prolonged treatment with inhaled steroids [33]. It seems unlikely that this effect could have been due to a decrease in LTD4 synthesis given the scant evidence that LTD4 has an important role in asthma [34]. However it is difficult to conceive how the blockade of production of cysteinyl leukotrienes could have had such a marked effect so rapidly. The study clearly needs to be repeated in larger numbers of subjects with treatment both given acutely and long-term. It would be helpful if the results could be confirmed with another leukotriene synthesis inhibitor or antagonist to demonstrate that the effect is due to interference with the leukotriene pathway rather than an unrelated effect of zileuton. If the results of these studies are also positive it will clearly lead to a re-evaluation of the role of leukotrienes in the pathophysiology of asthma and increased understanding about the link between airways inflammation and BHR.

References

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