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REVIEW

The role of thromboxane A_2 in the pathogenesis of airway hyperresponsiveness

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Airway hyperresponsiveness to a variety of bronchoconstrictor mediators and physical stimuli, such as exercise, is present in patients with asthma [1]. Inhalation of inflammatory stimuli such as allergens [2] or occupational sensitizing agents [3] in sensitized subjects, the atmospheric pollutant ozone [4], or the development of viral upper respiratory tract infections [5] can cause transient airway hyperresponsiveness, which can last days, weeks or occasionally months [6] and is associated with worsening symptoms of asthma [7].

Investigation of the pathogenesis of airway hyperresponsiveness has been most easily carried out in animals or humans by studying stimuli known to cause airway hyperresponsiveness. This is because administration of these stimuli can be carefully controlled in a laboratory setting. Those most extensively studied have been the inhaled allergens, toluene diisocyanate (TDI) or ozone both in humans [6, 8, 9], and in several animal models [10–13]. There are, however, several problems with this approach. For example, the mechanisms of airway hyperresponsiveness, even to the same stimulus, appear to differ between species [14, 15]. Also, the mechanisms causing acute airway hyperresponsiveness may be different to those causing persistent airway hyperresponsiveness in asthma. Thromboxane A_2 (TxA_2), may be an important mediator in the pathogenesis of airway hyperresponsiveness in animal models, and allergic responses as well as transient and persistent airway hyperresponsiveness in humans. This article will review the evidence that TxA_2 is involved in these responses.

Thromboxane A_2

Thromboxane A_2 (TxA_2) is a cyclooxygenase product of arachidonate metabolism. The compound was initially described by PIPER and VANE [16] in 1969 as contracting rabbit aorta in a bioassay, and was first characterized and named by HAMBERG *et al.* [17] in 1975. TxA_2 is known to be both a potent constrictor of smooth muscle, particularly vascular smooth muscle, and to cause platelet aggregation. TxA_2 was originally described as being released from platelets [17], but is now known to be released from other cells, including macrophages and neutrophils [18].

The biological half-life of TxA_2 is very short (approximately 30 s); therefore, implicating TxA_2 in disease processes has depended on measurement of its more stable metabolite Thromboxane B_2 (TxB_2) in biological fluids; on the use of the stable endoperoxides U44069 or U46619, which mimic most of the biological effects of TxA_2 and have been used as TxA_2 analogues; and on the use of inhibitors of TxA_2 synthesis and antagonists of the TxA_2 receptor. Using these techniques, TxA_2 has been implicated in the pathogenesis of airway hyperresponsiveness in dogs [19–22] and primates [23]; of the late cutaneous response to intradermal allergen [24] in humans; of the immediate response to inhaled allergen in dogs [25]; of the late asthmatic response after inhaled allergen in humans [26]; and of airway hyperresponsiveness in asthmatic subjects [27].

TxA_2 in the pathogenesis of airway hyperresponsiveness

Animal models

Studies examining the role of cyclooxygenase products of arachidonate in the pathogenesis of airway hyperresponsiveness were initially carried out using the cyclooxygenase inhibitor, indomethacin. These studies were performed in dogs with airway hyperresponsiveness after inhaled ozone. Indomethacin did not alter baseline airway responsiveness to inhaled acetylcholine, but did prevent the development of airway hyperresponsiveness after inhaled ozone [28]. Despite the absence of airway hyperresponsiveness, the magnitude of the inflammatory response, as measured by the numbers of neutrophils in the airway epithelium, was not altered by indomethacin. This suggested that a cyclooxygenase product was not responsible for the chemotaxis of acute inflammatory cells into the airways after inhaled ozone; however, a cyclooxygenase product was released during the inflammatory response which caused airway hyperresponsiveness. Subsequently, a reputed combined cyclooxygenase and lipooxygenase inhibitor, BW775c was also demonstrated to prevent the development of airway hyperresponsiveness after inhaled ozone in dogs [29]. Inhibition of cyclooxygenase by indomethacin also prevents the development of airway hyperresponsiveness

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in other species; for example, after C_{5a} des arg in rabbits [30], and after inhaled allergen in sheep [31]. Other investigators, however, demonstrated that BW775c, but not indomethacin, prevents airway hyperresponsiveness after inhaled ozone in guinea-pigs [32], suggesting that a lipooxygenase rather than a cyclooxygenase product was causing airway hyperresponsiveness in this species.

The cyclooxygenase product causing airway hyperresponsiveness after inhaled inflammatory stimuli in these animal models is most likely TxA_2. This is based on three lines of evidence. Firstly, a TxA_2 synthetase inhibitor prevents the development of airway hyperresponsiveness. Secondly, increased levels of TxB_2, the metabolite of TxA_2, can be measured in bronchoalveolar lavage (BAL) fluid from dogs with airway hyperresponsiveness after leukotriene B_4 (LTB_4). Thirdly, TxA_2 mimetics, such as U46619, can cause airway hyperresponsiveness.

A TxA_2 synthetase inhibitor, OKY 046 has been demonstrated to effectively inhibit the development of acetylcholine airway hyperresponsiveness after inhaled allergen [19], ozone [20], LTB_4 [21], and platelet activating factor (PAF) [22] in dogs, without changing baseline acetylcholine airway responsiveness or the influx of inflammatory cells after inhalation of each of these stimuli. These results implicated TxA_2 in causing airway hyperresponsiveness, but not in causing chemotaxis of inflammatory cells into the airways. One problem with interpretation of these results, however, is that inhibition of TxA_2 synthesis in other systems increases levels of other prostanoids, such as prostaglandin I_2 (PGI_2). Therefore, the inhibition of airway hyperresponsiveness after these stimuli may reflect the production of a protective prostanoid rather than inhibition of TxA_2.

Increased levels of TxB_2 have been demonstration in BAL fluid from dogs with airway hyperresponsiveness after inhaled LTB_4 [21]. The increase in TxB_2 was correlated with neutrophil counts in BAL. Significant increases were also seen in levels of prostaglandins E_2 and $F_{2\alpha}$ after inhaled LTB_4. OKY 046 inhibited not only the development of airway hyperresponsiveness, but also the rise in levels of TxB_2 in BAL, without altering the increase in prostaglandins E_2 and $F_{2\alpha}$ or the influx of neutrophils after inhaled LTB_4. The increase in TxB_2 in BAL may, however, be specific to LTB_4 challenge as no increase in TxB_2 could be found in BAL fluid from Ascaris-sensitive dogs challenged with allergen, although there was a large increase in prostaglandin D_2 (PGD_2) and histamine [33].

The final piece of evidence is the demonstrated that inhaled subthreshold concentrations of the TxA_2 mimetic, U46619, can increase airway responsiveness to acetylcholine in dogs [20]. This effect was not seen with another contractile agonist, histamine. These studies all suggest that TxA_2 release in the airways is important in the pathogenesis of airway hyperresponsiveness after inhalation of inflammatory stimuli such as ozone, allergen, PAF and LTB_4 in dogs. Studies in primates have demonstrated that another TxA_2 mimetic, U44069, increases airway responsiveness to acetylcholine and that this effect was abolished by the TxA_2 receptor antagonist, L655, 240 [23].

Mechanism of action of TxA_2 in the airways

The mechanism by which TxA_2 causes airway hyperresponsiveness is not yet known, but possible mechanisms include presynaptic modulation of acetylcholine release, or an effect on airway smooth muscle.

TxA_2 was demonstrated to modulate acetylcholine release in airways initially by MUNOZ *et al.* [34] using the TxA_2 mimetic U46619, which increased the response to field stimulation in trachealis muscle. This effect lasted more than 60 min. No increase in the response to exogenous acetylcholine by U46619 was demonstrated, suggesting that the augmentation was occurring presynaptically, through increased acetylcholine release in response to field stimulation. Further support for this hypothesis was provided by TAMAOKI *et al.* [35], who demonstrated that aggregated platelets in an organ bath released TxA_2. The TxA_2 transiently increased the responses to field stimulation and this effect was prevented by a TxA_2 receptor antagonist. Once again, the response to an exogenous cholinergic agonist was not altered by the released TxA_2.

The increased response to field stimulation may not, however, necessarily be caused by increased amounts of acetylcholine released from the nerve terminal. For example, SERIO and DANIEL [36] have demonstrated that U46619 increases the response to electrical field stimulation in canine trachealis, an effect that is antagonized by a TxA_2 receptor antagonist. The effect on electrical field stimulation was not seen with leukotriene B_4 or D_4 or prostaglandin D_2. The effect of U46619, however, was not associated with increases in the amplitude or duration of associated excitatory junctional potentials (EJPs), but rather with an increase in the number of secondary oscillations which follow the EJP. These results suggest that TxA_2 may not enhance the initial amount of acetylcholine release *per se*, but rather the duration of release or may improve the propagation of activity through the muscle.

Presynaptic modulation of acetylcholine release may also be altered in dogs with airway hyperresponsiveness after inhaled ozone [37]. When trachealis muscle from dogs with airway hyperresponsiveness *in vivo* was studied in the organ bath, the response to electrical field stimulation was increased when compared to control dogs. By contrast, the responses to exogenous acetylcholine were no different between the two groups of dogs. These results suggested that trachealis muscle itself was no different in dogs with airway hyperresponsiveness after ozone, but that the amounts of acetylcholine being released in response to nerve stimulation was increased. These results are consistent with the known effects of TxA_2 on acetylcholine release in canine trachealis already discussed. Therefore, throm-

boxane, released as part of the airway inflammatory response after inhaled ozone, may be responsible for the increased response to nerve stimulation in the ozone treated tissues.

Recent studies in our laboratories have confirmed the results of WALTERS *et al.* [37] that the responses to electrical field stimulation are increased in ozone treated dogs when compared to control dogs [38]. However EJPs, whether measured by the single or double sucrose gap, were no different between the two groups of dogs. These results were qualitatively similar to the results of SERIO and DANIEL [36] on the effects of U46619 on the responses to field stimulation. These results suggest that something other than an increase in the initial amount of acetylcholine released is responsible for the increased response to field stimulation in muscle strips from dogs with airway hyperresponsiveness *in vivo*.

TxA_2 can act on specific receptors on airway smooth muscle. This is because U44069 constricts airway smooth muscle, an effect which is abolished by TxA_2 receptor antagonists [23, 36]. There is, however, no evidence that TxA_2 can increase responsiveness of smooth muscle to other constrictor agonists *in vitro*.

Studies in human subjects

Studies examining the importance of specific mediators in the pathogenesis of asthma are complicated, when compared to studies in animal models, by the lack of potent, specific mediator antagonists, and by the difficulties in measuring the mediator or its metabolite at its site of action in the airways. For example, indomethacin, which has been extensively used to implicate cyclooxygenase products in the pathogenesis of disease, inhibits the production of not only potentially harmful mediators such as TxA_2 and prostaglandin D_2, but also potentially useful mediators in asthmatic airways, such as prostaglandin E_2 [39]. These difficulties have been partly overcome in studies examining the response to allergen in the skin.

TxA_2 has been implicated in the pathogenesis of allergen-induced late cutaneous response in human subjects. GRONNENBERG *et al.* [40] have demonstrated partial inhibition of the late cutaneous response to anti-IgE after pretreatment with indomethacin. Also, an increase in TxB_2 levels has been demonstrated in skin blister fluid during the late cutaneous response, 6 h after injection of allergen [41]. These investigators have also shown that a TxA_2 synthesis inhibitor, dazoxiben, inhibits the late cutaneous response [24]. Thus, it appears that TxA_2 may be responsible for some of the manifestations of the late cutaneous, but not the early cutaneous response, after injected allergen.

TxA_2 is released from lung tissue in allergic asthmatic subjects after stimulation with specific allergen [42]. However, sulphidopeptide leukotrienes, released at the same time, appear to be more important in causing contractile responses after stimulation with allergen *in vitro* [42].

Attempts to measure TxB_2 during asthma or following allergen challenge have led to conflicting results. SHEPHARD *et al.* [26] have demonstrated increased levels of TxB_2 in plasma following allergen challenge. However, plasma TxB_2 measurements must be viewed with caution because of the possibility of local platelet generation of TxB_2 and measurements should be confirmed by assaying the 2, 3-dinor-metabolite of TxB_2 which cannot come from platelet activation alone. In a small series of atopic asthmatics, challenged with allergen bronchoscopically, TxB_2 levels were not elevated when compared to a sham challenge. However, in a patient with status asthmaticus, increased levels of TxB_2 in lavage fluid was found, but this could have been due to *ex vivo* generation of TxB_2 from alveolar macrophages. In a larger series of patients with either acute asthma or undergoing allergen challenge, urinary levels of TxB_2 and 2, 3-dinor-TxB_2 were measured. In both groups the levels of these mediators were within the normal range. This lack of evidence for TxA_2 generation does not rule out its importance, as high local levels generated in the region of the smooth muscle may not lead to a significant increase in total body turnover of the metabolite.

Cyclooxygenase products have been implicated in the pathogenesis of allergen-induced early asthmatic [43] as well as late asthmatic responses [44, 45]. This has been done by pretreating subjects with several different cyclooxygenase inhibitors. For example, JOUBERT *et al.* [45] reported that pretreatment with indomethacin inhibited the late response in 10 out of 11 subjects studied, without having a major effect on the early response. More recent studies, however, have not confirmed these observations on either allergen-induced early or late responses. Pretreatment with indomethacin (100 $mg \cdot day^{-1}$) administered in a double-blind, randomized, cross-over fashion did not influence either the early or late asthmatic responses [46]. These results suggested that cyclooxygenase products, including TxA_2 were not important mediators in causing allergen-induced asthmatic responses.

There is evidence which implicates a cyclooxygenase product, possibly TxA_2, in the pathogenesis of airway hyperresponsiveness in asthmatic subjects. Indomethacin significantly inhibits the development of airway hyperresponsiveness after inhaled allergen in allergic subjects [46]. This suggests that a cyclooxygenase product is involved in the pathogenesis of airway hyperresponsiveness after inhaled allergen. In addition, the TxA_2 synthetase inhibitor, OKY 046, administered orally, reduces acetylcholine airway hyperresponsiveness in stable asthmatic subjects (although these studies were uncontrolled), while a lipooxygenase inhibitor had no effect in these subjects [27]. Thus, TxA_2 may be an important mediator in the pathogenesis of airway hyperresponsiveness either in stable asthma or after inhaled allergens. Recent studies, however, have examined the effect of a thromboxane synthetase inhibitor, CGS 12970, on airway responsiveness measured 4 h and 6 h after allergen challenge. CGS 12970 had no effect on either the early or late responses after inhaled allergen. In addition, there was no effect on airway

hyperresponsiveness to inhaled histamine measured at 4 h and 6 h post-allergen [47].

Chronic smokers also have an increase in airway response to inhaled spasmogens, which may also be due in part to airway inflammation. It has been observed that smokers have a nearly two-fold increase in urinary 2, 3-dinor-TxB_2 [48]. In a group of smokers with airway hyperresponsiveness the urinary levels of 2, 3-dinor-TxB_2 were no different from a group of smokers with normal airway responsiveness, nor was there any correlation between the level of airway responsiveness and excretion of the metabolite. Furthermore, treatment with the cyclooxygenase inhibitor, flurbiprofen 150 mg for 3 days did not change airway responsiveness despite abolishing the excretion of the metabolite [49]. It appears unlikely, therefore, that TxA_2 is responsible for the airway hyperresponsiveness found in some smokers.

Conclusions

The studies described have suggested that TxA_2 is released from inflammatory cells in the airways and may be important in causing airway hyperresponsiveness after a number of inflammatory stimuli in dogs. The action of TxA_2 is through a presynaptic effect on airway cholinergic nerves and also possibly a postsynaptic effect on airway smooth muscle. A cyclooxygenase product of arachidonate metabolism (possibly TxA_2), is also important in causing airway hyperresponsiveness in other species, such as rabbits and sheep.

In human subjects, the role of TxA_2 in causing airway hyperresponsiveness is much less clear. A cyclooxygenase product appears to be involved in allergen-induced airway hyperresponsiveness. Attempts to measure abnormal TxA_2 production in asthma has so far been unsuccessful. Studies with two thromboxane synthetase inhibitors have provided conflicting results. However, synthetase inhibitors may not be the ideal drugs to use, as reactive endoperoxides may be released during synthetase inhibition; therefore, thromboxane receptor antagonists need to be studied. It is clear that a large amount of research needs to be done to confirm and extend these observations before the precise role of thromboxane in the pathogenesis of asthma is clarified.

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