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Asthma Mediators: Current Views

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Asthma is characterized by a complex inflammatory response involving resident (e.g. mast cells, macrophages, nerves), recruited (e.g. lymphocytes, eosinophils, monocytes) and structural cells (e.g. epithelium, airway smooth muscle, fibroblast). These cells can synthesize and secrete a vast number of mediators which may contribute to the bronchoconstriction, submucosal-gland secretion, vasodilation, bronchial wall oedema, recruitment of inflammatory cells, airway re-modelling and bronchial hyper-responsiveness observed in asthma. The role of individual mediators, in the context of asthma has been greatly facilitated by the discovery of highly potent and selective mediator antagonists.

Given the complex nature of the pathophysiology of asthma and the vast array of potential mediators which are released and thought to contribute to this process, it is perhaps not surprising that few mediator antagonists have been successfully developed for the treatment of asthma, perhaps with one exception to date (Drazen et al 1999). However, it is clear that many new candidate mediators are being investigated for their potential role in asthma and in the future, drugs affecting the activity of cytokines, chemokines and growth-related peptides may prove successful. The current standing of more recently studied mediators will be discussed, although for historical purposes, more traditional mediators will also be included. For a more detailed review of the many potential mediators thought to play a role in asthma one should consult a recently published review on this subject by Barnes et al (1998).

Histamine

Histamine is the classical mediator that has been extensively studied in the context of allergy and asthma. It is stored in granules within mast cells and basophils and can be released under immunological conditions following the cross-linking of antigen to high affinity IgE receptors present on the surface of mast cells and basophils or by non-immunological stimuli (e.g. compound 48/80, calcium ionophore, substance P and hypo-osmolar solutions). Histamine concentrations are elevated in bronchoalveolar lavage fluid of asymptomatic mild asthmatics (Liu et al 1990) and following antigen challenge (Wenzel et al 1988; Liu et al 1991). The acute bronchoconstriction observed following antigen challenge is attenuated by selective H_1-receptor antagonists (Holgate & Finnerty 1989). These findings confirm that the acute release of histamine following an allergic or nonallergic insult may lead to bronchoconstriction. Histamine released within the airway also has the potential to increase vascular permeability (Braude et al 1984), induce vasodilation (Kaliner et al 1981) and stimulate submucosal gland secretion (Shelhamer et al 1980), effects which are thought to be mediated following activation of H_2-receptors. There is evidence that histamine may also stimulate sensitised afferent nerves. Thus, following viral infection, the bronchoconstriction response to inhaled histamine is attenuated by muscarinic blockade, suggesting that reflex activation of cholinergic nerves occurs (Empey et al 1976). With regard to inflammatory cells, histamine has been shown to activate eosinophils but the receptor subtype involved could not be clearly defined (Raible et al 1994) and there is evidence that histamine can downregulate the function of immune cells via an H_2-receptor-dependent mechanism.

Antihistamines are widely used in the treatment of allergic diseases where the release of histamine is thought to play an important role in the symptoms associated with hayfever, urticaria and mild asthma (Holgate & Finnerty 1989). However, it is clear that a number of H_1-receptor antagonists including cetirizine, terfenadine, ebastine, oxatimide, loratidine and ketotifen demonstrate anti-inflammatory activity unrelated to H_1-receptor blockade. For example, cetirizine inhibits f-met-leu-phe (FMLP)- and platelet activating factor (PAF)-induced chemotaxis of eosinophils (Charlesworth et al 1989; Okada et al 1994) and superoxide generation by eosinophils (Okada et al 1994),

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inhibits FMLP-, leukotriene (LT) B_4 (LTB_4)-induced chemotaxis of lymphocytes and monocytes (Jinquan et al 1995) and also inhibits eosinophil survival in-vitro (Sedgwick & Busse 1997). Similarly, oxatimide inhibits antigen-induced degranulation of human lung mast cells and basophils in-vitro (Patella et al 1996). The mechanism by which these drugs inhibit inflammatory cell function is unclear but may be related to stabilisation of cell membranes and interference with intracellular calcium mobilisation.

A number of clinical studies have reported that cetirizine can attenuate the wheal and flare response following intradermal injection of antigen, while having effect on neither the late cutaneous response nor the attendant eosinophilia and deposition of eosinophil cationic protein (ECP) (Atkins et al 1997; Zweiman et al 1997). Similarly, 3 weeks' treatment with cetirizine failed to attenuate early- and late-phase responses, although the effect of cetirizine on bronchial hyperresponsiveness following antigen challenge is controversial (de Bruin Weller et al 1994; Bentley et al 1996). Nonetheless, 15-days' treatment with cetirizine significantly reduced the expression of intracellular adhesion molecule (ICAM)-1 and eosinophil number in scrapings from nasal mucosa in children sensitive to house dust mite (Fasce et al 1996). Following 26 weeks' treatment, cetirizine has also been shown to reduce a number of clinical symptoms in patients with perennial asthma (Aaronson 1996), which suggests that these drugs appear to be more effective in mild forms of allergic disease.

Lipid Mediators

Prostanoids

Immediately following acute antigen challenge of asthmatic subjects, increased levels of prostaglandin (PG) $F_{2\alpha}$, PGD_2 and thromboxane (TX) B_2 are detected in bronchoalveolar lavage fluid (Murray et al 1986; Liu et al 1990; Dworski et al 1994), most likely derived from the activation of mast cells, although other potential sources of these prostanoids include macrophages and airway epithelium. Non-steroidal anti-inflammatory drugs (NSAIDs) have a modest inhibitory action against the acute bronchoconstriction response to allergens (Sestini et al 1997, 1999) which suggests that mediators, in addition to prostanoids, play a greater role in the acute bronchoconstriction following allergen challenge. However, when inhaled, these prostanoids cause bronchoconstriction (Fish et al 1984; Hardy et al 1984; Saroea et al 1995) and more interestingly, increase airways responsiveness to spasmogens unrelated to alterations in airway calibre (Heaton et al 1984; Fuller et al 1986) which suggest that prostanoids may play a greater role in modulating airways responsiveness. Indeed, the increase in airways responsiveness following antigen challenge is attenuated following inhalation of NSAIDs in some asthmatic subjects (Sestini et al 1997, 1999).

Prostanoids are synthesized by cyclooxygenase (COX) of which there are two isoforms. COX1 is constitutively expressed in a number of cells including mast cells and airway epithelium (Mitchell et al 1995). Various pro-inflammatory cytokines stimulate the induction of COX2 in human airway epithelium (Mitchell et al 1994) and smooth muscle (Johnson & Knox 1997) in culture suggesting that during inflammation, COX2 expression may be augmented. However, immunohistochemical examination of bronchial biopsies from subjects with mild to severe asthma revealed the presence of both COX1 and COX2 in airway epithelium, without a preferential increase in COX2 expression (Demoly et al 1997).

While the profile of prostanoids formed by COX1 and COX2 are similar, the role of PGE_2 in the context of airway inflammation is complex. PGE_2 relaxes human airway smooth muscle in-vitro (Knight et al 1995) and induces bronchodilation in asthmatic subjects when inhaled (Pavord et al 1993). Consistent with the view that PGE_2 may inhibit the inflammatory response, studies have shown that inhaled PGE_2 inhibits the development of the late asthmatic response unrelated to functional antagonism of airway smooth muscle contraction (Pavord et al 1993; Gauvreau et al 1999a) and attenuates the attendent increase in sputum eosinophilia (Gauvreau et al 1999a). Furthermore, PGE_2 inhibits the proliferation of human airway smooth muscle (Johnson & Knox 1997). The potential beneficial effect of PGE_2 on airway inflammation in asthma might explain in part why NSAIDs can induce exacerbation of asthma in aspirin-sensitive asthmatic subjects. The administration of aspirin has been shown to result in an elevation in the levels of leukotrienes, while reducing the levels of PGE_2 and TXB_2 in bronchoalveolar lavage fluid (Szczeklik et al 1996).

Other studies have shown that PGE_2 may have pro-inflammatory properties: PGE_2 induces cough in healthy and asthmatic subjects (Choudry et al 1989) and might play a role in the development of the allergic response by downregulating interferon (IFN)γ and interleukin (IL)-12 production from T lymphocytes and monocytes, respectively, thereby promoting T helper 2 lymphocyte development (Betz & Fox 1991; Snijdewint et al 1993; van der

Pouw Kraan et al 1995). Furthermore, NSAIDs can partially attenuate the late asthmatic response in some subjects (Sestini et al 1999). The potential anti- and pro-inflammatory properties of PGE_2 may reflect activation of different prostanoid receptor subtypes on different cells.

The indiscriminate inhibition of anti- and pro-inflammatory prostanoids following administration of NSAIDs, perhaps explains why NSAIDs have limited therapeutic activity in asthma. Other strategies, including the development of selective prostanoid-receptor antagonists and enzyme inhibitors, have been investigated for their potential use in the treatment of asthma. The TXA_2 antagonist BAY u3405 produced a modest decrease in airways responsiveness to methacholine following 2 weeks' treatment in asthmatics (Aizawa et al 1996) but was ineffective against bradykinin-induced bronchoprovocation following a single oral administration (Rajakulasingam et al 1996). Similarly, the TXA_2 antagonist, GR32191 was ineffective against methacholine responsiveness in adult asthmatics following 3 week's treatment (Stenton et al 1992). These studies suggest that TXA_2 antagonists are unlikely to suppress baseline airways hyperresponsiveness in asthmatics.

The TXA_2 synthetase inhibitor ozagrel (OKY-046) reduced cough sensitivity to capsaicin (Fujimura et al 1995) and bronchoconstriction to acetaldehyde (Myou et al 1994) in asthmatics, indicating a possible role for TXA_2 in sensitisation of afferent nerves. In contrast, airways responsiveness to methacholine was not significantly altered following 1 week of treatment with UK-38,485 (Gardiner et al 1993). Similarly, although acute treatment with CGS 13080 attenuated the acute bronchoconstrictor response to antigen, the late asthmatic response and attendant bronchial hyperresponsiveness was not inhibited (Manning et al 1991). Whether PGE_2 receptor selective agonists or antagonists will be of benefit in asthma remains to be established.

Leukotrienes

Cysteinyl leukotrienes, including LTC_4, LTD_4 and LTE_4, are endogenous bioactive lipid mediators derived from the 5-lipoxygenase pathway in mast cells, eosinophils and macrophages. They posses potent pro-inflammatory actions resulting in increased vascular permeability, mucus secretion and bronchial hyperresponsiveness, they are responsible for activation and recruitment of inflammatory cells and are very potent spasmogens of human airway smooth muscle (Drazen et al 1999). The cysteinyl leukotrienes are known to activate two receptors, $CysLT_1$ and $CysLT_2$, and the biological activity of the cysteinyl leukotrienes, in the context of asthma, is mediated via activation of $CysLT_1$ receptor which has recently been cloned (Lynch et al 1999).

Elevated levels of LTC_4 are found in bronchoalveolar lavage fluid following antigen challenge (Wenzel et al 1990) and inhalation of LTC_4, LTD_4 (Adelroth et al 1986) and LTE_4 (Arm et al 1988) induces bronchoconstriction in asthmatic subjects. Similarly, the $CysLT_1$ receptor antagonist zafirlukast attenuated acute bronchoconstriction to allergen challenge (Taylor et al 1991; Dahlen et al 1994). These studies provide convincing evidence of IgE-dependent synthesis and release of leukotrienes during acute exacerbation of asthma.

LTD_4 did not increase airways responsiveness to methacholine, as measured by changes in sensitivity (Bel et al 1987; Mulder et al 1999), although an increase in the degree of airway narrowing was observed (Bel et al 1987). This may be a consequence of an increase in airway wall thickening, or a change in airway smooth muscle reactivity, stimulated by leukotrienes and thereby leading to increased reactivity of the airways to spasmogens (Bel et al 1987). In contrast, LTC_4, LTD_4 and LTE_4 increased the sensitivity of the airways to inhaled histamine (O'Hickey et al 1991). While the mechanism of this latter effect remains to be established, it is known that leukotrienes may alter the excitability of afferent nerves (Undem & Weinreich 1993; McAlexander et al 1998) thereby increasing the sensitivity of the airways to indirect acting stimuli. Alternatively, LTD_4 has been shown to promote the pulmonary recruitment of eosinophils in an animal model, by an IL-5-dependent manner (Underwood et al 1996), which could lead to an exacerbation of airways responsiveness. Clinical studies have suggested that leukotrienes may increase eosinophil number in biopsies (Laitinen et al 1993) and sputum (Diamant et al 1997), although this is not a consistent finding (Mulder et al 1999). Furthermore, acute administration of the leukotriene antagonist montelukast, while attenuating the development of the late asthmatic response, did not appear to inhibit eosinophil number or activation in sputum (Diamant et al 1999) and suggests that leukotrienes are not the major signal for eosinophil recruitment or activation in asthma.

The 5-lipoxygenase inhibitor zileuton was effective against bronchoconstriction induced by exercise (Meltzer et al 1996), cold air (Israel et al 1990) and reduced airways responsiveness to distilled water and histamine (Dekhuijzen et al 1997), but was ineffective against bronchoconstriction following antigen challenge (Hui et al 1991) in

asthmatics. Furthermore, in a small study, zileuton attenuated both airways and blood eosinophilia in nocturnal asthmatics (Wenzel et al 1995). Similarly, the 5-lipoxygenase activating protein (FLAP) inhibitors, MK-0591 (Diamant et al 1995) and MK-886 (Friedman et al 1993), attenuated the early and late asthmatic response following antigen challenge but not the attendant increase in airway responsiveness to spasmogen.

The $CysLT_1$ receptor antagonists zafirlukast (ICI 204,219), montelukast (MK-0476) and pranlukast (SB 205312, ONO 1078) have also been assessed clinically. Zafirlukast potently inhibited bronchoconstriction to inhaled LTD_4 challenge, attenuated early- and late-phase bronchoconstriction to inhaled allergen (Taylor et al 1991; Dahlen et al 1994) and following exercise (Finnerty et al 1992) and attenuated bronchoconstriction to inhaled sulphur dioxide (Lazarus et al 1997). Similarly, pranlukast a potent antagonist of LTD_4 induced bronchoconstriction (O'Shaughnessy et al 1997), attenuated aspirin-induced asthma (Yamamoto et al 1994) and antigen-induced acute bronchoconstriction (Taniguchi et al 1993) and had a modest effect against airways responsiveness to methacholine following 1 week of treatment (Fujimura et al 1993). Together these studies support the view that leukotriene antagonists improve pulmonary function and clinical symptoms in a subpopulation of asthmatic subjects, are well tolerated and appear to be safe (Drazen et al 1999).

Peptide Mediators

A number of peptide mediators, including bradykinin, sensory neuropeptides (substance P, neurokinin A and calcitonin gene related peptide (CGRP)) and endothelin, are released within the lung and have a wide range of pharmacological activity. Several studies in man have shown that these mediators may contribute toward various aspects of the inflammatory response in asthma.

Bradykinin

The kinins, bradykinin and lysyl–bradykinin are synthesized from high (plasma) and low (tissue) molecular weight kininogens respectively, by the action of kininogenases. Lysyl–bradykinin is in turn, converted to bradykinin by the action of aminopeptidase-N (Proud 1998). Bradykinin has a short plasma half-life and is terminated by the action of angiotensin-converting enzyme (ACE). Bradykinin produced within the airway wall is terminated by neutral endopeptidase (NEP) present within the epithelium and airway smooth muscle.

Kininogenase activity has been detected in bronchoalveolar lavage fluid in asymptomatic asthmatics (Christiansen et al 1987) and both kininogenase activity and kinin levels were increased following antigen challenge (Christiansen et al 1992). The release of kinins within the airways could lead to the activation of bradykinin receptors including, B_1 receptors whose expression is regulated by inflammatory cytokines and B_2 receptors present on various cells within the airway wall including vascular endothelium, airway smooth muscle, submucosal glands, nerves and airway epithelium (Mak & Barnes 1991). When inhaled, bradykinin produces modest (if any) bronchoconstricition in healthy subjects, but is a potent bronchoconstrictor agonist in asthmatic subjects (Fuller et al 1987a). The bronchoconstriction produced in response to inhaled bradykinin is atropine sensitive (Fuller et al 1987a) and possibly involves prostaglandins (Polosa et al 1997), but not TXB_2 (Rajakulasingam et al 1996). Interestingly, the bronchoconstriction to inhaled bradykinin is augmented following ingestion of the nitric oxide synthase inhibitor, N-(G)-monomethyl-L-arginine (LNMMA), suggesting that nitric oxide functionally antagonizes the bronchoconstriction to bradykinin in asthmatic subjects (Ricciardolo et al 1996).

Clinical studies suggest that bradykinin induces bronchoconstriction via activation of afferent nerves and subsequent reflex bronchoconstriction. Animal studies reveal that bradykinin stimulates a sub-population of afferent nerves, C-fibres (Fox et al 1993), and mediates the release of sensory neuropeptides from these (Saria et al 1988). Interestingly, the increase in airway responsiveness to bradykinin following antigen challenge is greater than that observed with methacholine and, moreover, persists for several days (Berman et al 1995). Furthermore, airways responsiveness to bradykinin, but not methacholine, correlates with the number of eosinophils in bronchoalveolar lavage fluid, bronchial biopsies and sputum (Roisman et al 1996; Polosa et al 1998). This suggests that bradykinin-dependent pathways are upregulated following antigen challenge or in clinical asthma but it is unclear whether this is a consequence of increased expression of B receptors on afferent nerves or upregulation of afferent activity, or a combination of both.

The effect of bradykinin-receptor antagonists in asthma is only beginning to be explored; a 4-week treatment with the bradykinin antagonist, icatibant (HOE 140) has been shown to provide a small improvement in various clinical indices (Akbary et al 1996). Clinical studies with nonpeptide antagonists remain to be investigated.

Sensory neuropeptides

In mammals, the preprotachykinin-I (PPT-I) gene encodes substance P and neurokinin A while PPT-II encodes neurokinin B (Nawa et al 1983, 1984; Kotani et al 1986; Krause et al 1987). Alternate splicing of the PPT-I gene results in the formation of three mRNAs designated α-, β- and γ-PPT. Post-translational processing of α-, β- and γ-PPT mRNA yields substance P and, from the two latter forms of mRNA, neurokinin A. Furthermore, neuropeptide K and neuropeptide-γ are (N-terminally) extended forms of neurokinin A produced by β- and γ-PPT mRNA, respectively, while neurokinin A (3–10) is produced from β- and γ-PPT mRNA. Alpha- and beta-calcitonin gene-related peptide (α-CGRP and β-CGRP) are products of two distinct calcitonin genes (Amara et al 1982, 1985) and expression of mRNA for all of these sensory neuropeptides has been demonstrated in primary afferent neurones (Gibson et al 1988; Minami et al 1989; Rethelyi et al 1989).

More recently, studies employing retrograde techniques have revealed that almost all afferent nerves within guinea-pig trachea arise from cell bodies within the nodose ganglion, yet most of the nerves which contain neuropeptides have cell bodies that arise from the jugular ganglion (Kummer et al 1992). This latter finding is consistent with an earlier study in which vagal section above, but not below, the nodose ganglion resulted in significant loss in substance P-like immunoreactivity in guinea-pig (Lundberg et al 1983b). In human studies, neuropeptides, including substance P, CGRP, neurokinin A, neuropeptide Y and vasointestinal peptide (VIP), have been detected in the lung. Immunohistochemical techniques reveal that fibres containing substance P are sparsely distributed within the bronchial epithelium, around blood vessels, bronchial smooth muscle and local tracheobronchial ganglia (Lundberg et al 1984; Hislop et al 1990; Komatsu et al 1991). It has even been suggested there is an absence of substance P-like immunoreactivity in the lung, despite demonstrable substance P in other tissues (Laitinen et al 1983). However, this is unlikely since substantial amounts have been extracted from human lung using a high-performance liquid chromatography (HPLC) technique (Lilly et al 1995).

Both substance P and neurokinin A contract human bronchi (Lundberg et al 1983; Advenier et al 1987), yet the vanilloid-receptor agonist, capsaicin elicits only a modest contractile response and is at least 2–3 orders of magnitude less potent than in guinea-pig (Lundberg et al 1983; Honda et al 1991; Chitano et al 1994). Capsaicin can also mediate an inhibitory response that is not dependent on the release of sensory neuropeptides (Chitano et al 1994), thereby potentially masking the excitatory action of this substance in these in-vitro studies. To date, no study has convincingly demonstrated contractile responses in human airway tissue which are secondary to release of sensory neuropeptides from excitatory non-adrenergic non-cholinergic (eNANC) nerves (Lundberg et al 1983a; De Jongste et al 1987).

Intravenous (Fuller et al 1987b; Evans et al 1988) or aerosolised (Joos et al 1987) substance P produces marginal changes in lung function in healthy individuals, while neurokinin A produces a small bronchoconstrictor response (Evans et al 1988). Various histochemical, immunohistochemical and biochemical studies have revealed that neutral endopeptidase is found in the lung of guinea-pigs (Djokic et al 1989; Kummer & Fischer 1991) and man (Johnson et al 1985), localised predominantly in the epithelium, and is responsible for the degradation of tackykinins (Nadel 1991). Bronchoconstriction in response to inhaled neurokinin A in healthy individuals (Cheung et al 1992) was augmented by previous inhalation of the neutral endopeptidase inhibitor, thiorphan, which may explain the propensity of asthmatics to bronchoconstrict in response to inhaled neurokinin A (Joos et al 1987). However, thiorphan (Cheung et al 1993) and phosphoramidon, another neutral endopeptidase inhibitor (Crimi et al 1994), augmented the bronchoconstrictor response to neurokinin A in mild asthmatics to a similar degree to that observed in healthy individuals (Cheung et al 1993). It seems likely, therefore, that asthmatics are intrinsically more responsive to neurokinin A as a manifestation of the mechanism that determines differential responsivity between asthmatic and normal individuals for other indirect-acting stimuli. Anticholinergic drugs have a modest inhibitory effect on the bronchoconstrictor response to both substance P (Crimi et al 1990) and neurokinin A (Joos et al 1988) in asthmatics, suggesting that sensory neuropeptides may, in part, activate afferent nerves, thereby facilitating reflex bronchoconstriction.

Three distinct types of tachykinin receptors exist, based on comparisons of the potencies of tachykinin agonists in the ileum and the cardiovascular system in various animal species (Maggi 1995; Bertrand & Geppetti 1996). The rank order of potency of mammalian tachykinins is: substance P > neurokinin A > neurokinin B, for NK_1-receptors; neurokinin A > neurokinin B > substance P for NK_2-receptors, and neurokinin B > neurokinin A > substance P for NK_3-receptors. Autoradiographic studies have detected binding sites for substance P in airway smooth muscle in the rabbit

(Black et al 1990). However, little, if any, binding for substance P was detected in airway smooth muscle in man (Goldie 1990; Walsh et al 1994) even though binding sites for substance P have been reported in one study of human airway smooth muscle (Carstairs & Barnes 1986). Whether methodological differences can account for these discrepancies is unclear but would seem unlikely, given that substance P binding sites were clearly detected in the microvasculature and submucosal glands of humans (Goldie 1990; Walsh et al 1994). Functional studies have revealed that tachykinins contract human isolated bronchi via NK_2-receptors (Naline et al 1989; Advenier et al 1992).

Studies using capsaicin have implicated sensory nerves as a common pathway by which various stimuli induce bronchial hyperresponsiveness and studies with neurokinin-receptor antagonists have been consistent with this proposition, their being able to abrogate bronchial hyperresponsiveness induced by several stimuli (Spina et al 1998). Animal models have provided a wealth of information concerning the possible mechanisms by which sensory nerves might alter responsiveness. There are some analogous studies which demonstrate that these mechanisms may also operate in man. For instance, it has been claimed that substance P-containing nerves are more abundant in lungs obtained at autopsy from asthmatics as compared with healthy individuals (Ollerenshaw et al 1991), although this observation has not been confirmed in other studies (Howarth et al 1991; Chanez et al 1998). Using HPLC, a reduction in substance P-like immunoreactivity was observed in the lungs of individuals who died of asthma or who were undergoing thoracotomy, compared with age-matched non-diseased subjects (Lilly et al 1995). Similar changes have been reported in other diseases. In rheumatoid arthritis, there appears to be a loss of substance P- and CGRP-like immunoreactivity in sensory nerves in synovial tissue (Mapp et al 1990), while individuals with idiopathic cough who have increased sensitivity to capsaicin have increased levels of CGRP and, to a lesser extent, substance P-immunoreactivity in nerves within bronchial biopsies as compared with healthy subjects (O'Connell et al 1995).

This circumstantial evidence implicating release of sensory neuropeptides in asthma is consistent with the detection of increased substance P-like immunoreactivity in bronchoalveolar lavage fluid in atopic asthmatics as compared with healthy individuals (Nieber et al 1992). The level of substance P-like immunoreactivity in bronchoalveolar lavage was further increased in atopic asthmatics who had experienced an acute reaction to inhaled allergen (Nieber et al 1992). An elevated level of substance P-like immunoreactivity has also been detected in the sputum of patients with asthma or chronic bronchitis, as compared with healthy individuals, following hypertonic saline inhalation (Tomaki et al 1995). These findings are complimented by the observation that chronic treatment with capsaicin reduced symptoms and vascular reactivity in patients with severe chronic non-allergic rhinitis (Lacroix et al 1991) suggesting that sensory neuropeptides are involved in the increased responsiveness of the upper respiratory tract.

Other studies have documented possible changes in neurokinin receptor expression in asthma. An increase in mRNA transcripts for neurokinin-1 (Adcock et al 1993) and neurokinin-2 (Bai et al 1995) receptors was demonstrated in lung tissue from asthmatics as compared with non-asthmatics. This may be in response to local release of neuropeptides and consequent neuropeptide receptor tachyphylaxis. However, evidence of an increase in the expression of neuropeptide mRNA in sensory nerves or an increase in afferent activity, or both, awaits documentation in man. With the availability of neurokinin antagonists, a number of studies have begun to explore the role of sensory neuropeptides in asthma. The non-selective NK_1- and NK_2-antagonist, FK224 has been reported to inhibit (Ichinose et al 1992), or be marginally effective (Schmidt et al 1996) against, bradykinin-induced bronchoconstriction and ineffective against neurokinin A-induced bronchoconstriction in asthmatics (Joos et al 1996). The latter outcome questions the utility of this antagonist to evaluate the role of neuropeptides in asthma. The selective NK_2-antagonist, SR48968 did attenuate neurokinin A-induced bronchoconstriction in asthma (Van Schoor et al 1998) and the NK_1-receptor antagonist, FK888 improved recovery from exercise-induced airway narrowing in asthmatics (Ichinose et al 1996), although the NK_1-selective antagonist, CP99994 was without effect on hypertonic saline-induced bronchoconstriction and cough in asthmatics (Fahy et al 1995). While the current generation of neurokinin receptor antagonists have proved disappointing, strategies aimed at reducing afferent activity may offer a novel approach in attempts to suppress cough and bronchial hyperresponsiveness in asthma (Spina et al 1998).

Endothelin

Endothelins were originally discovered as potent vasoconstrictor peptides and a wide range of studies have shown that these peptide mediators demonstrate pharmacological activity in the air-

ways and may play a role in the pathophysiology of asthma (Hay 1998). There are three endothelin peptides, each encoded by three distinct genes (Inoue et al 1989). Endothelin-1 is formed as a proteolytic product from the precursor peptide, preproendothelin-1 via an intermediary product, big-endothelin-1. The conversion of big-endothelin-1 to endothelin-1 occurs via the action of endothelin converting enzyme (ECE). The expression of mRNA for the endothelins and ECE has been documented in human bronchial epithelial cells (Saleh et al 1997) and can be upregulated by a variety of pro-inflammatory cytokines (Endo et al 1992; Shima et al 1995). Thus, the epithelium may serve as a potential source for endothelins, particularly during inflammatory situations, and thereby play a role in airway inflammation (Hay 1998). The endothelins are metabolised by neutral endopeptidase, an enzyme also located within airway epithelium (Hay 1989).

At least two receptor subtypes have been found for the endothelins, characteristic of G protein-coupled receptors. Autoradiographic studies have documented the presence of ET_B receptors in airway smooth muscle in healthy (Knott et al 1995) and asthmatic subjects (Goldie et al 1995) with no obvious difference in distribution or density in asthma. Endothelin is a potent contractile agonist of human airway smooth muscle (Henry et al 1990; Knott et al 1995) and augments cholinergic nerve-mediated responses in human airways in-vitro (Fernandes et al 1996), both effects mediated via the activation of ET_B receptors. Furthermore, while endothelin did not stimulate the proliferation of human airway smooth muscle, it augmented the proliferative response to epidermal growth factor (EGF) via an ET_A-receptor-dependent manner (Panettieri et al 1995). Few studies have examined the pro-inflammatory action of endothelins in the airways (Hay 1998). ET_A- but not ET_B-receptor antagonists attenuated allergen-induced recruitment of eosinophils in a murine model of inflammation (Fujitani et al 1997), in part by increased production of IFNγ from pulmonary lymphocytes.

Elevated levels of endothelin have been detected in bronchoalveolar lavage fluid from asthmatic subjects not taking glucocorticosteroid therapy (Redington et al 1995), consistent with an increase in the expression of immunoreactive endothelin in epithelium from biopsies taken from asthmatic subjects (Springall et al 1991; Redington et al 1997a). However, acute bronchoconstriction to allergen inhalation (Redington et al 1997c) or hypertonic saline (Makker et al 1999) does not appear to be associated with the release of endothelin-1. This is perhaps not surprising as this mediator is not stored and requires de-novo synthesis, which may occur several hours after acute challenge. Endothelin-1 is a potent bronchoconstrictor agonist in asthmatic subjects but has no effect in healthy subjects (Chalmers et al 1997). The effect of endothelin-receptor antagonists in the context of asthma awaits investigation.

Nitric Oxide

It is almost two decades since the discovery that the endothelium released a soluble factor which relaxed vascular smooth muscle (Furchgott & Zawadzki 1980), that was termed endothelium-derived relaxing factor, and later identified as nitric oxide (NO) (Ignarro et al 1987; Palmer et al 1987). NO is derived from the amino acid, L-arginine by the enzyme, nitric oxide synthase (NOS), of which there exists the calcium-dependent constitutive isoforms, endothelium (e)NOS or NOS3 and the neural (central and peripheral) isoform, nNOS or NOS1. These isoforms are also expressed in tissue other than their original designation. Thus, nNOS is also present in human bronchial epithelium (Kobzik et al 1993). A third isoform (iNOS or NOS2), only expressed following an inflammatory insult, is less dependent upon calcium for activation and produces significant quantities of NO. This latter isoform is thought to play a role in pathophysiological situations.

In the lung, NOS3 is localised to endothelial cells in the bronchial circulation and within the epithelium (Shaul et al 1994) and NOS1 is predominantly localised to cholinergic nerves (Fischer et al 1993). In asthmatic airways, NOS2 is predominantly found within the airway epithelium (Hamid et al 1993; Saleh et al 1998) and inflammatory cells, notably macrophages, neutrophils and eosinophils (Saleh et al 1998). Clinical studies have detected the presence of NO in exhaled air of asthmatic subjects (Kharitonov et al 1994), in increased concentrations during the late asthmatic response (Kharitonov et al 1995), supporting the view that during inflammation, expression of NOS2 is increased.

The functional consequences of NO in the airways has been investigated in a number of studies. In human airways it appears that NO is the neurotransmitter which mediates the non-adrenergic non-cholinergic inhibitory response (Belvisi et al 1992), consistent with the localisation of NOS immunoreactivity to cholinergic nerves (Ward et al 1995). NO is a potent vasodilator of the pulmonary circulation (Higenbottam 1995) and may either inhibit (Erjefalt et al 1994) or promote (Bernareggi et al

1997) plasma protein extravasation in the airways, this latter action being dependent upon the expression of NOS2. It has recently been proposed that NO may promote the development of the atopic state by suppressing the function of T-helper (Th)1 lymphocytes which act as a braking mechanism for the development of Th2-mediated responses (i.e. atopy) (Barnes & Liew 1995). Indeed, mice lacking the ability to express NOS2 i.e. NOS2 knockout mice, are characterized by the presence of elevated levels of the Th1 cytokine, IFNγ, which would tend to suppress the development of the atopic phenotype; these mice are associated with reduced levels of eosinophils recruited into the airways following allergen challenge (Riffo-Vasquez et al 1999; Xiong et al 1999). It is unclear whether this is due to a reduction in Th2 commitment (Barnes & Liew 1995). Alternatively, NO has been shown to promote eosinophil chemotaxis (Ferreira et al 1996) and inhibit eosinophil apoptosis (Beauvais et al 1995; Hebestreit et al 1998), events which would not occur in NOS2-deficient mice.

The NOS inhibitor, L-nitro arginine methyester (L-NAME) failed to attenuate the early and late asthmatic response following antigen challenge in asthmatic subjects (Taylor et al 1998). The level of expired NO was significantly decreased following treatment with L-NAME, which probably reflects inhibition of NOS1 and NOS3, since there was a lack of increase in expired NO during the late asthmatic response (8–10 h) in the placebo arm of the study. This, suggests that NOS2 expression was not increased during this time-period and therefore makes interpretation of the data difficult. However, 21 h after allergen challenge, there was a significant increase in expired NO which was not evident in the L-NAME treated group, possibly reflecting an increase in NOS2 expression. Whether the development of more selective NOS2 inhibitors will prove of greater benefit in asthma, requires further investigation.

Cytokines

Different T-lymphocyte functions (cytolysis, induction of apoptosis, B-cell help and inflammatory-cell recruitment) are mediated by different T-lymphocyte subsets that can be identified by the effector molecules (cytokines) they secrete (Mosmann et al 1986). CD4 T lymphocytes are classified as T helper 1 (Thl) cells, which provide immunity to pathogens such as *Mycobacterium tuberculosis*, and as T helper 2 (Th2) cells, that give rise to allergic inflammation. Thl lymphocytes secrete IFNγ, IL-2 and tumour necrosis factor (TNF)-β; Th2 lymphocytes secrete cytokines such as IL-4 and IL-13, which switch on B cells to produce IgE (Snapper & Paul 1987; Punnonen et al 1993), and IL-5, which promotes eosinophilic inflammation. Thl and Th2 lymphocytes produce cytokines IFN-γ and IL-4, respectively, that inhibit the growth and function of the other subset.

IgE-dependent mechanisms can account for the recruitment of eosinophils to the airways and bronchial hyperresponsiveness following antigen challenge of asthmatic subjects (Fahy et al 1997), though it is clear that mechanisms additional to IgE play a role in this regard. Allergic reactions in the airways are caused by IgE-sensitised mast cells and by CD4-positive Th2 , whose activation leads to the infiltration of inflammatory cells, notably eosinophils, and the subsequent tissue damage (Erb 1999). Increased numbers of CD4-positive T lymphocytes which express mRNA for IL-4 and IL-5, but not IFN-γ, have been observed in the airway submucosa and sputum of patients with asthma, and during allergen-induced late-phase asthmatic reactions where they are associated with increased numbers of eosinophils (Corrigan et al 1995; Till et al 1995; Ying et al 1997; Olivenstein et al 1999).

The use of murine models has provided a considerable wealth of knowledge concerning the role of T lymphocytes and individual cytokines in the inflammatory response. Thus, pulmonary recruitment of eosinophils is significantly impaired 24–48 h following antigen challenge of mice previously treated with a monoclonal antibody directed against CD4 (Nakajima et al 1992). Interestingly, the recruitment of eosinophils to the lung 9 h after antigen challenge was not inhibited in this model and suggests that CD4 T lymphocyte-independent mechanisms (i.e. IgE-dependent mechanisms) could play a role in the early recruitment of eosinophils to the airways. CD4-positive T lymphocytes are also implicated in bronchial hyperresponsiveness (Gavett et al 1994; Hogan et al 1998). A recent study has demonstrated that the adoptive transfer of Th0 and Th2 clones into Severe Combined Immunodeficiency (SCID) mice induces both pulmonary eosinophilia and bronchial hyperresponsiveness following antigen challenge (Hansen et al 1999). In contrast, the adoptive transfer of Th1 cell clones into SCID mice resulted in a monocytic infiltrate into the lung without any attendant bronchial hyperresponsiveness (Hansen et al 1999). Similarly, the adoptive transfer of T lymphocytes from genetically hyperresponsive mice can increase airways responsiveness in hyporesponsive recipient mice (De Sanctis et al 1997). The T-lymphocyte factors responsible for these finding remain to be established. However, the role of various cytokines released from Th2 lymphocytes, including IL-4, IL-5 and IL-13, upon antigen-induced eosino-

philia and bronchial hyperresponsiveness, have been investigated in a number of studies using knockout models and monoclonal antibodies directed against these cytokines.

Although IL-4 has been shown to be important for Th2 lymphocyte commitment and isotype switching of B cells to the IgE phenotype (Kopf et al 1993), the role of IL-4 in allergen induced recruitment of eosinophils and bronchial hyperresponsiveness is controversial. Thus, eosinophil recruitment is significantly attenuated in IL-4 gene-disrupted mice (Brusselle et al 1995; Coyle et al 1995), in mice that have been treated with monoclonal antibodies to IL-4 during antigen immunisation (Coyle et al 1995) or before antigen challenge (Lukacs et al 1994) and in mice treated with IL-4-receptor antibodies before antigen challenge (Gavett et al 1997). In contrast, other studies have shown that treatment with antibodies directed against IL-4 either before antigen sensitisation (Corry et al 1996) or antigen challenge (Coyle et al 1995; Corry et al 1996) had no effect on eosinophil recruitment to the airways. Interestingly, a recent study has shown that eosinophil recruitment to the lungs still occurs in IL-4-deficient mice (Hogan et al 1997) and in mice following the adoptive transfer of Th2-cell clones from IL-4-deficient mice (Cohn et al 1998). However, in both cases the migration of eosinophils from the tissue to the lumen appears to be impaired, although the mechanism of this phenomenon remains to be established (Hogan et al 1997; Cohn et al 1998). Similarly, both IL-4-dependent (Brusselle et al 1995; Corry et al 1996) and -independent (Hogan et al 1997, 1998; Cohn et al 1998) mechanisms contribute toward the bronchial hyperresponsiveness observed in murine models of inflammation. It would therefore appear that both IL-4-dependent and -independent mechanisms can be expressed in different murine models of inflammation. These differences cannot be solely explained by the use of different strains of mice since a number of the conflicting data has arisen using mice of a similar genetic background (Brusselle et al 1994, 1995; Hogan et al 1997). A more plausible explanation is that under the different experimental conditions employed, CD4 T lymphocytes may induce antigen bronchial hyper-responsiveness and eosinophilia via IL-4-dependent and -independent pathways. This conclusion is further substantiated by the finding that the development and commitment of a subpopulation of Th2 lymphocytes is not dependent upon IL-4 (Hogan et al 1998; Lohning et al 1998).

Another cytokine which has received considerable interest is IL-5. Monoclonal antibodies directed against IL-5 attenuate eosinophil recruitment in allergic mice and in bronchial hyper-responsiveness (Nakajima et al 1992; Eum et al 1995; Foster et al 1996; Hamelmann et al 1997). Conversely, eosinophil recruitment is compromised and bronchial hyperresponsiveness inhibited in IL-5 gene-disrupted mice immunised to antigen (Foster et al 1996) and if IL-5 is over-expressed in the lung, then bronchial hyperresponsiveness is observed in non-sensitized mice (Lee et al 1997). However, in some circumstances, IL-5 is not obligatory for the development of bronchial hyper-responsiveness, although it is consistently clear that CD4 T lymphocytes are a necessary requirement for the recruitment of eosinophils and bronchial hyperresponsiveness in these murine models (Hogan et al 1998). Therefore, other factors released from the T lymphocyte may be important and it has recently been documented that monoclonal antibodies directed against IL-13 are sufficient to inhibit antigen-induced bronchial hyper-responsiveness (Grunig et al 1998; Wills-Karp et al 1998). Nevertheless, the role of IL-13 in the recruitment of eosinophils to the airways remains controversial (Grunig et al 1998; Wills-Karp et al 1998). It is clear that considerably redundancy exists in the action of these cytokines and the development of selective cytokine antagonists for the treatment of asthma will be a challenge. However, strategies which selectively target Th2 lymphocytes may prove more successful.

Studies are beginning to address the role of cytokines in asthma. The inhalation of human recombinant IL-5 in asthmatic subjects was associated with a 3-fold increase in airways sensitivity to methacholine, a 6-fold increase in sputum eosinophil number and a 3-fold increase in sputum ECP levels, 24–48 h following challenge (Shi et al 1998). In contrast, a monoclonal antibody directed against IL5, while significantly attenuating eosinophil numbers in sputum and blood, failed to alter the late asthmatic response or bronchial hyperresponsiveness to methacholine in asthmatic subjects (Leckie et al 1999). This study suggests that IL5-independent pathways may be involved in the late asthmatic response and baseline bronchial hyper-responsiveness in asthma. It remains to be established whether other monoclonal antibodies directed against IL5 prove more effective and what effect these antibodies have in the clinical setting. Clearly, further studies are required to elucidate the exact role of IL5 in asthma.

Chemokines

Chemokines are a group of small-molecular-weight peptides (8–10 kDa) which have a number of bio-

logical effects, including chemotaxis, immunoregulation and cell growth, and are classified into CXC, CC and C families (Alam 1997; Mantovani 1999). Of particular interest is the role of CC chemokines in the context of asthma as they are potent chemoattractants for eosinophils, basophils, monocytes and T lymphocytes.

The CC chemokines—macrophage inflammatory protein (MIP)1α, monocyte chemotactic protein (MCP)-1 and RANTES (regulated on activation, normal T-cell expressed and secreted)—are elevated in bronchoalveolar lavage fluid in symptomatic (Alam et al 1996) but not asymptomatic asthmatic subjects (Cruikshank et al 1995; Holgate et al 1997). Furthermore, 4–6 h after endobronchial allergen challenge of mild asthmatic subjects, there is a significant increase in the levels of MIP1α, MCP-1 and RANTES in lavage fluid (Cruikshank et al 1995; Holgate et al 1997). Similarly, the number of eosinophils positive for eotaxin and RANTES was significantly elevated in the sputum 7 h after antigen challenge of mild asthmatic subjects (Gauvreau et al 1999b) and demonstrate that exacerbation of asthma leads to the synthesis and release of various chemokines which can contribute to the recruitment of inflammatory cells to the airways.

The expression of mRNA, but not protein, for RANTES was elevated in bronchial biopsies in mild asymptomatic asthmatic subjects compared with controls (Berkman et al 1996) and the number of cells positively expressing mRNA for RANTES and MCP-3 was significantly increased in mild to moderate symptomatic asthmatic subjects compared with healthy controls (Humbert et al 1997). Increased expression of eotaxin mRNA and immunoreactive protein has also been described in bronchial biopsies (Mattoli et al 1997) and increased expression of eotaxin and MCP-4 mRNA has been shown in both central and peripheral airways of asthmatic subjects compared with non-asthmatic controls (Lamkhioued et al 1997; Taha et al 1999). The source of these chemokines is predominantly epithelial and within the submucosa they are localised to macrophages, T lymphocytes and eosinophils. Inflammatory cytokines, including IL1β and TNFα, and bacterial lipopolysaccharide can induce the synthesis of various chemokines (Lilly et al 1997; Mantovani 1999).

The CC chemokine, eotaxin is a potent chemoattractant for eosinophils (Garcia Zepeda et al 1996; Kitaura et al 1996; Ponath et al 1996) and basophils (Yamada et al 1997) mediated via selective activation of the G protein-coupled CC chemokine receptor (CCR)3 (Daugherty et al 1996; Kitaura et al 1996). Recent studies have shown that CCR3 is also present on Th2 lymphocytes and activation of this receptor is implicated in the recruitment of these cells to sites of inflammation (Sallusto et al 1998). In a murine model of tissue eosinophilia, targeted disruption of the eotaxin gene resulted in an attenuation of the early- (18 h) but not late (48 h)-phase recruitment of eosinophils to the lung following antigen challenge (Rothenberg et al 1997), suggesting that substances additional to eotaxin are involved in the recruitment of eosinophils to the airways. It is clear that a number of different chemokines may act at different stages of the inflammatory response and thereby contribute toward the recruitment of eosinophils and expression of bronchial hyper-responsiveness (Gonzalo et al 1998). Furthermore, antibodies directed against eotaxin suppressed constitutive and allergen-induced chemoattractant activity in bronchoalveolar lavage fluid (Humbles et al 1997) while treatment of skin sites with antisera to eotaxin inhibited the accumulation of radiolabelled eosinophils following antigen challenge, as did desensitisation of CCR3 with eotaxin and blockade of the receptor with RANTES (Teixeira et al 1997). A monoclonal antibody (7B11) directed against CCR3 inhibited binding, chemotaxis and calcium influx of eosinophils induced by eotaxin, eotaxin-2, RANTES, MCP-2, MCP-3 and MCP-4 (Heath et al 1997; Bochner et al 1999), and suggests the possibility of developing CCR3 selective antagonists. More recently, a novel CC chemokine, macrophage-derived chemokine, was shown to stimulate chemotaxis of human eosinophils via a CCR3- or CCR4-independent pathway (Bochner et al 1999). The role of this chemokine in the context of airway inflammation remains to be established.

Growth Factors

The characteristic features of asthma include deposition of collagen beneath the basement membrane, goblet cell hyperplasia, angiogenesis and increased thickness of airway smooth muscle. The structural remodelling that occurs in asthma, is thought to underlie the baseline hyper-responsiveness found in this disease. A variety of growth factors are thought to play a role in altering the structure of the airways.

The expression of a number of growth factors, including platelet derived growth factor (PDGF), transforming growth factor (TGF) and epidermal growth factor (EGF), in bronchial biopsies from asthmatic subjects has been investigated. The levels of PDGF and PDGF receptors were not different in biopsies between healthy and asthmatic subjects

(Aubert et al 1994; Chanez et al 1995). In contrast, the expression of mRNA for TGFβ and immunoreactivity of protein was significantly increased in the epithelium and submucosa of biopsies taken from asthmatic patients than from healthy subjects (Minshall et al 1997; Vignola et al 1997). Indeed, there was a significant correlation between the number of cells positive for TGFβ and the severity of asthma and subepithelial fibrosis (Minshall et al 1997; Vignola et al 1997), suggesting that this growth factor may play an important role in subepithelial fibrosis seen in this disease. Eosinophils, fibroblasts and epithelial cells are the major sources of TGFβ (Magnan et al 1997; Minshall et al 1997; Vignola et al 1997). These studies are consistent with the finding of a modest increase in the levels of immunoreactive TGFβ in bronchoalveolar lavage fluid 24 h after antigen challenge of mild asthmatic subjects (Redington et al 1997b) and presumably reflect the recruitment of eosinophils to the airways (Minshall et al 1997). Although the level of immunoreactive TGFβ is elevated in asthma, it is not exclusive to this disease and is also elevated in chronic bronchitis (Vignola et al 1997). Hence, the exact role of this growth factor in the context of asthma requires further investigation. The expression of EGF and EGF receptor, detected in airway epithelium, glands and smooth muscle was increased in biopsies from asthmatic subjects (Vignola et al 1997; Amishima et al 1998).

A number of in-vitro studies have shown that PDGF is a potent mitogen of human airway smooth muscle (Hirst et al 1996). TGFβ is a potent stimulant for fibroblast mitogenesis and is important in wound healing and fibrosis (Border & Noble 1994), plays a pleiotrophic role in the immune system (Torre-Amione et al 1990) and inhibits proliferation of airway smooth muscle (Cohen et al 1997). EGF induces airway smooth muscle proliferation (Cerutis et al 1997) and ET-1 potentiates EGF-induced airway smooth muscle proliferation (Panettieri et al 1996).

Proteases

Tryptase is a mast-cell serine protease released following IgE stimulation (Schwartz et al 1981). The physiological role for tryptase is unclear but it is known to affect fibroblast proliferation, degrade fibrinogen, generate C3a (Harvima & Schwartz 1993), stimulate mucus secretion (Sommerhoff et al 1989) and degrade sensory neuropeptides (Caughey et al 1988; Tam & Caughey 1990). Thus, mast cell tryptase could play a role in regulation of haemostasis, mucus secretion and vascular permeability.

The proteases, thrombin and trypsin specifically regulate cells by cleaving members of a growing family of proteinase-activated receptors (PARs) which couple to heterotrimeric G-proteins (Dery et al 1998). Thrombin cleaves PAR-1 and trypsin and mast-cell tryptase cleave PAR-2, exposing tethered ligand domains that bind to and activate the cleaved receptors which may play a role in inflammation and repair processes. Both PAR-1 and PAR-2 have been found in human airways, localised to the epithelium and airway smooth muscle (Cocks et al 1999; Hauck et al 1999). Functional studies reveal that PAR-2-activating peptides induce an epithelium and cyclooxygenase-dependent relaxation of human airway smooth muscle, while PAR-1-activating peptides induce a contractile response (Cocks et al 1999; Hauck et al 1999). Animal studies reveal that thrombin-receptor-activating peptides and PAR-1-activating peptides induce a platelet-dependent bronchoconstriction (Cicala et al 1999), while activation of PAR-2 inhibits bronchoconstriction (Cocks et al 1999). However, PAR-2-activating peptides have been shown to induce acute inflammatory response and neutrophil accumulation in rat hind paw (Vergnolle et 1999). Furthermore, thrombin induces proliferation of human airway smooth muscle (Panettieri et al 1995) and tryptase is mitogenic for fibroblasts (Ruoss et al 1991; Cairns & Walls 1997), smooth muscle cells (Brown et al 1995) and epithelial cells (Cairns & Walls 1996). The definitive role of PAR in these responses awaits confirmation with selective agonists and antagonists.

Elevated tryptase levels are evident in asthma, even in the absence of deliberate antigen challenge (Wenzel et al 1988; Bousquet et al 1991), which may contribute toward bronchial hyper-responsiveness. Incubation of tracheal smooth muscle with canine tryptase augments smooth muscle contractility in-vitro (Sekizawa et al 1989) and airways responsiveness to carbachol is increased following aerosolisation of tryptase in sheep (Molinari et al 1996).

The mast-cell tryptase inhibitor, APC-366 inhibited antigen-induced late-phase response and bronchial hyper-responsiveness to carbachol in sheep (Clark et al 1995) and bronchial hyperresponsiveness to aerosolised tryptase (Molinari et al 1996). Similarly, lactoferrin, which disrupts the quaternary structure of tryptase, also attenuated antigen-induced late response and bronchial hyperresponsiveness in allergic sheep (Elrod et al 1997). The role of protease inhibitors in the context of asthma remains to be evaluated.

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