Occasional review

Bradykinin and asthma

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Many mediators have been implicated in the pathophysiology of asthma[1 2] but the role of individual mediators will become apparent only with the use of potent and selective antagonists or synthesis of inhibitors, which are now becoming available for many mediators. Bradykinin has long been considered to be a mediator concerned in asthma, since the first demonstration of bronchoconstriction after inhaled bradykinin in asthmatic patients.[3] The recent development of potent bradykinin receptor antagonists[4–6] has raised questions about the role of bradykinin in the pathophysiology of asthma and the potential of bradykinin antagonists in the treatment of asthma.

Formation

Kinins are vasoactive peptides formed during the inflammatory response from the α_2 globulins high and low molecular weight kininogens by the action of kininogenases (figure 1). Kininogenases include plasma kallikrein and tissue kallikrein. High molecular weight and low molecular weight kininogens are derived from the same gene as a consequence of alternative splicing.[7] High molecular weight kininogen is present only in plasma, whereas low molecular weight kininogen also occurs in tissues. Two kinins are formed in man—the nonapeptide bradykinin (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg), which is generated from high molecular weight kininogen, and the decapeptide lysyl-bradykinin (kallidin), which is generated from low molecular weight kininogen. Kallidin is rapidly converted to bradykinin by the enzyme aminopeptidase-N.[8] There is evidence for kinin activity in bronchoalveolar lavage fluid from asthmatic patients[9] and bradykinin is likely to be formed from plasma that has exuded from the inflamed airways, by the action of plasma and tissue kallikreins. The concentration of kallikrein and kinins in bronchoalveolar lavage fluid increases after allergen challenge.[10] High molecular weight kininogen is the preferred substrate for plasma kallikrein, which is generated from the inactive prekallikrein by contact with certain negatively charged surfaces, including basement membrane components and proteoglycans, such as heparin, released from mast cells. Tissue kallikreins are produced in glandular secretions and release kinins from both high molecular weight and low molecular weight kininogens. Other proteases that may be produced by inflammatory cells may also generate kinins from kininogens. Mast cell tryptase is a weak kininogenase in vitro under conditions of low pH; it is unlikely that this occurs to any significant extent in vivo.[11] There is also some evidence that neutrophils and platelets may release proteases with kininogen activity.[12]

Receptors

Bradykinin exerts several effects on the airways, which are mediated via specific surface receptors. At least two subtypes of bradykinin (BK) receptor are recognised.[13] BK_1 receptors are selectively activated by kallidin and des-Arg-bradykinin, but they have been found only under certain experimental conditions, and these observations have usually been confined to rabbits.[14] The effects of bradykinin on airways are mediated via BK_2 receptors, and there is no evidence for functional BK_1 receptors. A BK_3 receptor has also been described in airway smooth muscle of sheep,[15 16] but there are some doubts about its existence, as it has been defined with weak antagonists. A BK_2 receptor from rat uterus has recently been cloned and has the typical seven transmembrane spanning segment structure common to all G protein receptors.[17] Northern analysis has shown strong expression in lung tissue. Pharmacological studies suggest that there may be subtypes of the BK_2 receptor.[18] The agonist [Thi^{5,8},D-Phe^{7}]bradykinin appears to distinguish a "neuronal" form, which is fully activated, and a "smooth muscle" form, which is only partially activated by this agonist. The availability of a specific cDNA probe for the BK_2 receptor should make it possible to discover whether there are true differences in BK receptors between tissues.

The distribution of BK_2 receptors has been mapped out in human and guinea pig lung by autoradiography with [^{3}H]bradykinin.[19] There is a high density of binding sites in bronchial and pulmonary vessels, particularly on endothelial cells. Epithelial cells, airway smooth muscle (particularly in peripheral airways), submucosal glands, and nerves are also labelled, indicating that bradykinin may have diverse effects on airway function. A particularly high density of labelling is observed in the lamina propria immediately beneath the

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Effects of bradykinin on airway function

Airway cells	*Effect*
Airway smooth muscle	Contraction (small airways > large airways?)
Nerves	Activation of C fibre endings Enhanced neuropeptide release from sensory nerves Increased cholinergic reflex mechanisms Cough
Bronchial vessels	Vasodilatation (endothelium dependent) Plasma exudation (direct and indirect)
Epithelium	Increased ion transport (via PGE_2) Release of bronchodilators (PGE_2)
Mucus	Increased mucus secretion

epithelium; it is not clear what cellular structures are labelled but a very similar pattern of labelling has been observed in other epithelialised structures.[20] The subepithelial binding sites may be on nerves and superficial blood vessels.

Effects of airways

Bradykinin has several potent effects on airway function, all of which are mediated via a BK_2 receptor (table).

AIRWAY SMOOTH MUSCLE

Inhaled bradykinin is a potent bronchoconstrictor in asthmatic patients, but has no effect even in high concentration in normal individuals,[21-23] suggesting an increased responsiveness of airway smooth muscle to bradykinin, as is observed with other spasmogens. In vitro bradykinin is only a weak constrictor of human airways, suggesting that its potent bronchoconstrictor effect in asthmatic patients is mediated indirectly. Bradykinin contracts airway smooth muscle in vitro,[24] but in guinea pig airways in vitro bradykinin has weak and variable effects, which are influenced by the presence of airway epithelium and by the activity of local degrading enzymes. Bradykinin causes relaxation of intact guinea pig trachea in vitro, but constricts airways if epithelium is removed mechanically.[25 26] Bradykinin releases the bronchodilator prostaglandin E_2 from epithelial cells[26] and removing the epithelium therefore reduces the functional antagonism, resulting in a bronchoconstrictor effect of bradykinin. Furthermore, the enzyme neutral endopeptidase 24·11 is strongly expressed on airway epithelial cells[27] and thus removal of the epithelium may reduce bradykinin metabolism. A combination of indomethacin (to inhibit PGE_2 formation) and phosphoramidon (which inhibits neutral endopeptidase) mimics the effect of removal of the epithelium.[25] Shedding of the epithelium is commonly observed in asthmatic airways and this could be a factor contributing to the increased bronchoconstrictor effect of bradykinin in asthma. The bronchoconstrictor effect of bradykinin in ferrets in vitro and in guinea pig in vivo is enhanced by the inhibition both of neutral endopeptidase by phosphoramidon and of angiotensin converting enzyme by captopril.[28 29]

Intravenous bradykinin causes intense bronchoconstriction in the guinea pig, which is strongly inhibited by indomethacin, suggesting that a bronchoconstrictor cyclooxygenase product (probably thromboxane) largely mediates this effect.[30] The bronchoconstrictor response to bradykinin instilled directly into the airways is not reduced by indomethacin, however, suggesting a different mechanism of bronchoconstriction after airway delivery of the mediator.[30] In airway inflammation it is likely that bradykinin would be formed at the airway surface from plasma kininogens exuded into the airway lumen from leaky superficial blood vessles. In human subjects inhibition of cyclooxygenase by aspirin or flurbiprofen similary has no effect on the bronchoconstrictor effect of inhaled bradykinin.[22 31] The bronchoconstrictor response to both intravenous and inhaled bradykinin in the guinea pig is mediated via a BK_2 receptor because the BK_2 receptor antagonists NPC 349 and HOE 140 inhibit the bronchoconstrictor response, whereas a BK_1 selective antagonist is ineffective.[33-34] In human airways the bronchoconstrictor effect of bradykinin is also likely to be mediated via a BK_2 receptor because the BK_1 selective agonist [desArg^9]-bradykinin has no effect on airway function in asthmatic patients.[23] The distribution of BK receptors in both guinea pig and human airways suggests that bradykinin may have a greater direct effect on the smooth muscle of peripheral airways than of central airways, and indicates that in more proximal airways the effects of bradykinin are more likely to be indirectly mediated.[19]

NEURAL EFFECTS

Perhaps the most important property of bradykinin is its ability to activate C fibre nociceptive sensory nerve endings. Bradykinin is the mediator of inflammatory pain,[35] and in the airways this may be manifest as cough and tightness of the chest, which are commonly observed after inhalation of bradykinin in patients with asthma.[22] Bradykinin stimulates bronchial C fibres in dogs.[36] In guinea pigs the bronchoconstrictor response to instilled bradykinin is reduced by atropine and by capsaicin pretreatment, which depletes neuropeptides from sensory nerves, indicating that both a cholinergic reflex and release of neuropeptides from sensory nerves play a part.[30] Indeed, a combination of atropine and capsaicin pretreatment largely abolishes the bronchoconstrictor response to instilled bradykinin, but has little effect on the bronchoconstrictor response to intravenous bradykinin (which is largely inhibited by indomethacin).[30] Bradykinin also releases tachykinins from perfused guinea pig lung[37] and rat trachea,[38] and enhances the bronchoconstrictor response to electrical field stimulation (mediated by release of endogenous tachykinins) in guinea pig bronchi in vitro.[39] The effect of bradykinin on airway sensory nerves is blocked by the BK_2 antagonist HOE 140. Single fibre recordings from sensory

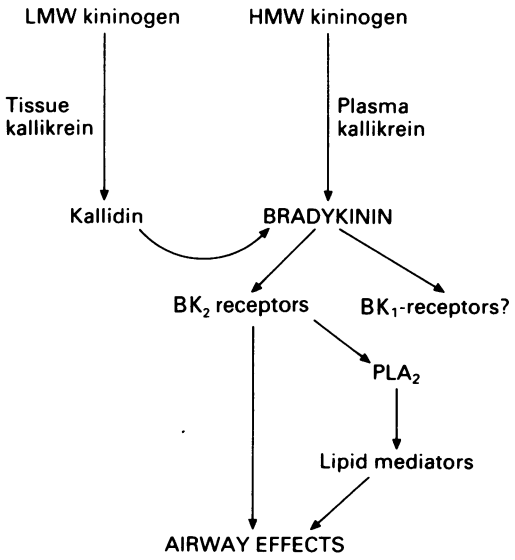

Figure 1 Bradykinin (BK) and its precursors: effects on the airways. LMW—low molecular weight; HMW—high molecular weight; PLA_2—phospholipase A_2

nerves of guinea pig airways indicate that bradykinin is a potent activator of C fibres, and that this is a direct action as it is not blocked by cyclooxygenase inhibition.[40] Bradykinin has no direct effect on the release of neurotransmitters from airway cholinergic nerves.[39]

In asthmatic patients the bronchoconstrictor response to bradykinin is also reduced by anticholinergic pretreatment, indicating that a cholinergic reflex is concerned.[22] Pretreatment with sodium cromoglycate and nedocromil sodium is very effective in inhibiting the airways response to bradykinin. This may indicate a role of C fibre activation in asthmatic airways,[41] as both drugs have been found to inhibit C fibres in animals.[42 43] Thus bradykinin may be an important mediator of cough and chest discomfort in asthma.

Bradykinin induces cough in normal and asthmatic subjects[44] and has been implicated in cough induced by angiotensin converting enzyme inhibitors, which is seen in about 10% of patients having long term treatment.[45] Cough induced by angiotensin converting enzyme inhibitors is reduced by cyclooxygenase inhibitors, suggesting that prostaglandins (such as PGE_2 or $PGF_{2\alpha}$) may play a part.[46] Endogenous bradykinin may stimulate the release of these prostaglandins in the larynx and trachea, leading to cough, though it is not clear why only some patients are affected.

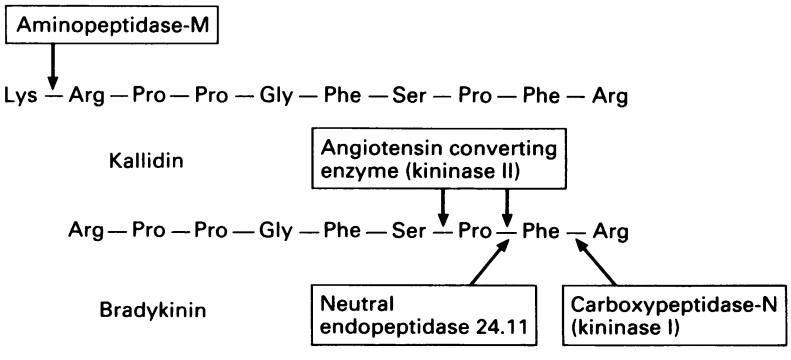

Figure 2 Degradation of lys-bradykinin (kallidin) and bradykinin by enzymes.

Angiotensin converting enzyme inhibitors do not worsen asthma, presumably because other enzymes, such as neutral endopeptidase, are more important in degrading bradykinin in airways. Indeed, a potent angiotensin converting enzyme inhibitor has been shown to have no effect on the bronchoconstrictor response to inhaled bradykinin in asthmatic patients, indicating that angiotensin converting enzyme is not of critical importance in degrading bradykinin in the lumen of human airways.[47]

VASCULAR ACTIONS

Bradykinin is a potent inducer of airway microvascular leak and causes a prolonged leakage at all levels of the airway. This is partly mediated via the release of platelet activating factor, because a PAF antagonist stongly inhibits the prolonged leak.[48] The immediate leakage response to bradykinin is partly mediated via the release of neuropeptides (probably substance P) from airway sensory nerves. The effect of bradykinin on leakage is mediated via BK_2 receptors, which are located on endothelial cells on postcapillary venules because BK_2 antagonists inhibit the leakage response.[33 34] The microvascular leakage induced by bradykinin is increased by inhibition of both neutral endopeptidase and angiotensin converting enzyme.[49]

Bradykinin is a potent vasodilator of bronchial vessels and causes an increase in airway blood flow.[50–52] This is consistent with the high density of bradykinin receptors on bronchial vessels,[19] and suggests that a major effect of bradykinin in asthma may be hyperaemia of the airways.

EFFECTS ON SECRETIONS

Bradykinin stimulates airway mucus secretion from canine and feline airways in vitro,[53 54] presumably indicating a direct effect of bradykinin on submucosal glands—and indeed autoradiographic mapping has shown BK_2 receptors on these glands.[19] Bradykinin also stimulates the release of mucus glycoproteins from human nasal mucosa in vitro.[54] Bradykinin stimulates ion transport in airway epithelial cells, which is mediated via the release of prostaglandins.[55]

Metabolism

Bradykinin is metabolised by several peptidases that may be present in the asthmatic airways (fig 2). Angiotensin converting enzyme (kininase 2) may be important for degrading bradykinin in the circulation as it is present in endothelial cells, but it may also be present in the airway tissue.[28] Angiotensin converting enzyme inhibitors potentiate both the bronchoconstrictor effect and the microvascular leakage produced by bradykinin,[29 56] suggesting that this may be the mechanism of cough induced by angiotensin converting enzyme inhibitors.

Neutral endopeptidase appears to be the most important enzyme in degradation of bradykinin in the airways. Phosphoramidon, which inhibits neutral endopeptidase, enhan-

ces the bronchoconstrictor effect of bradykinin both in vitro[25] and in vivo.[29 56] As neutral endopeptidase is expressed on airway epithelium, the shedding of airway epithelium in asthma may result in the enhanced airway responses to bradykinin seen in asthmatic patients.

A third enzyme, carboxypeptidase-N (kininase 1), may be important in degrading bradykinin in the circulation, but an inhibitor of this enzyme, DL-2-mercaptomethyl-3-guanidinoethylthiopropionic acid, does not have any effect on the bronchoconstrictor response to bradykinin in vivo.[29] Carboxypeptidase N converts bradykinin to [desArg^9]-bradykinin, which is selective for BK_1 receptors.[13] Aminopeptidase M, which converts lysyl-bradykinin to bradykinin, is widely distributed, so that kallidin is rapidly converted to bradykinin.

Bradykinin antagonists

Several peptide antagonists to bradykinin (BK_2 antagonists) have now been developed. The early antagonists were relatively weak and were rapidly degraded in tissues.[57 58] One such antagonist, D-Arg-[Hyp^3,Thi^{5,8},D-Phe^7]bradykinin (NPC 349), reduces the bronchoconstrictor and microvascular leakage response to bradykinin, but its effect is transient.[32 33] Suprisingly, in view of its short duration of action, the same antagonist appears to block allergen induced airway hyperresponsiveness in sheep, many hours after allergen exposure.[59] A related antagonist, [D-Arg^0-Hyp^3,D-Phe^7] bradykinin (NPC 567), is unable to inhibit the effect of bradykinin on nasal secretions, even when given at the same time as bradykinin,[60] presumably because of rapid local metabolism. More recently a potent antagonist of bradykinin, D-Arg[Hyp^3,Thi^5,D-Tic^7, Oic^8] bradykinin (HOE 140), has been described,[4 5] which not only is potent but also has a long duration of action in animals in vivo as it is resistant to enzymatic degradation. This antagonist is potent at inhibiting the bronchoconstrictor and the microvascular leakage response to bradykinin[34] and the effect of bradykinin on airway sensory nerves.[39] Other potent bradykinin antagonists have been developed, such as D-Arg[Hyp^3, Thi^5, D-Tic^7, Tic^8]bradykinin (NPC 16731),[6] and there is now a search for non-peptide antagonists.

A role for bradykinin in asthma?

Although the role of bradykinin in asthma is still not clear, the development of potent and stable BK_2 receptor antagonists offers the possibility of clarifying its role in airway disease in the near future.[4 5] Bradykinin is generated in asthmatic airways by the action of various kininogenases generated in the inflammatory response on high molecular weight kinogen present in the exuded plasma and on low molecular weight kinogens secreted in the airways. The degradation of bradykinin may be impaired in the airways if neutral endopeptidase is down regulated in asthmatic airways or epithelial shedding occurs.[27]

Bradykinin has many effects on the airway that are relevant to asthma. Perhaps the most important property of bradykinin is its ability to activate nociceptive nerve fibres in the airway because these may mediate the cough and chest tightness that are such characteristic symptoms of asthma. This effect of bradykinin may be enhanced by hyperaesthesia of sensory nerves in the airways that have been sensitised by inflammatory mediators. Inhalation of bradykinin in asthmatic patients has effects rather closely mimicking an asthma attack; in addition to wheezing, patients observe chest tightness, coughing, and sometimes itching under the chin, which are common sensory manifestations during an exacerbation of asthma.

The contribution of bradykinin to asthma will be determined only with the use of potent and specific bradykinin antagonists, which are now in clinical development. As many mediators may contribute to the pathophysiology of asthma it is difficult to predict how useful bradykinin antagonists will be; they may be of particular value in controlling asthma symptoms, but they are unlikely to be as effective as β agonists or corticosteroids.

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