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Review article

Role of the kinin-kallikrein pathway in allergic diseases

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R. Polosa

Institute of Respiratory Diseases, University of Catania, Catania, Italy

Dr R. Polosa
Institute of Respiratory Diseases
University of Catania
Via Passo Gravina, 187
95125 Catania
Italy

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Allergic diseases affect approximately 30–40% of the population of industrialized countries, with the prevalence of these disorders constantly increasing. More worryingly, despite the advent of improved therapeutic strategies, there has been no decline in the morbidity and mortality of these diseases over the last 10 years. Inflammatory mediators such as histamine, prostaglandins, and leukotrienes are generally considered to contribute to the pathogenesis of allergic disorders by a variety of mechanisms, including influx and subsequent activation of inflammatory cells, dilation of postcapillary venules, excitation of sensory nerve endings, and stimulation of other cellular structures (2). Their presence has been demonstrated in conjunction with immunologic stimulation in man, and, when exogenously administered, they induce many of the allergic-like symptoms (2, 41, 47, 88).

While several mediators have been proposed as playing a decisive role in the pathogenesis of asthma, rhinitis, and associated allergic disorders, technical difficulties in the analytic evaluation of many mediators or their metabolites at their site of action and the lack of potent and specific mediator antagonists have prevented conclusive evidence being obtained of a prominent role for any single mediator so far investigated. However, in recent years, with improved assay technologies and an increased awareness of the mechanisms regulating kinin levels, accumulating evidence seems to suggest that the activation of the kallikrein-kinin system may be of pivotal importance in the pathogenesis of allergic diseases. Three main points favor the view that kinins play a role in the inflammatory response. Firstly, they have actions which reproduce the cardinal signs and symptoms of acute inflammation, including vasodilation, increased vascular permeability, and stimulation of sensory nerves. Secondly, kinins have been found in increased amounts at the site of allergic tissue injury. Thirdly, local conditions related to tissue trauma and inflammation, such as the increased pH of the edematous fluid, favor the accumulation of kinins. This paper briefly reviews current knowledge of the potential role of kinins in the pathogenesis of allergic disorders, particularly asthma and rhinitis.

Biochemical pharmacology of kinins

Kinins are naturally occurring vasoactive oligopeptides formed *de novo* in body fluids and tissues during inflammatory processes. They are generated from α_2-globulin precursor proteins called kininogens (high-mol.-wt kininogen (HMWK) and low-mol.-wt kininogen (LMWK)), through proteolytic cleavage by a variety of enzymes, the most important of which are tissue and plasma kallikreins (74). While plasma kallikrein generates bradykinin, tissue kallikreins are unique in that they hydrolyze two dissimilar bonds within kininogens to release lysyl-bradykinin (kallidin). Tissue kallikrein has also been reported to be present in both the upper and lower airways in man (4, 10), and therefore they may be of particular relevance in kinin generation in inflammatory events of the airways.

Three kinins have been reported to exist in man,

bradykinin, lysyl-bradykinin (kallidin), and methionyllysyl-bradykinin (74). They all share the *C*-terminal nonapeptide sequence of bradykinin (Fig. 1). However, it is now accepted that methionyllysyl-bradykinin is a laboratory artifact (34); therefore bradykinin and kallidin are the only physiologically relevant kinins in man. Once generated, kinins promote both intra- and extracellular physiologic functions in a large number of physiologic systems, the latter being effected through interaction with specific cell surface receptors named B_1 and B_2 (74). These receptors are defined by a unique agonist potency series of kinin analogs, B_1 receptors being stimulated by [desArg^9]-bradykinin >> Bradykinin = Kallidin, while the B_2 receptors have a potency series of Bradykinin = Kallidin >> [desArg^9]-bradykinin.

Virtually all tissues and biologic fluids contain specific peptidases (kininases) that can degrade kinins and therefore limit their actions (24). Although hydrolysis of kinins by plasma peptidases has been reasonably well delineated, the full profile of peptidases on cells in human tissues remains to be determined. Kinin degradation is mainly initiated by the action of carboxypeptidase N (kininase I) and angiotensin-converting enzyme – ACE (kininase II) (Fig. 1). Carboxypeptidase N has been shown to degrade kinins by removal of the *C*-terminal arginine (ARG) residue to yield the desARG metabolites, [desArg^9]-bradykinin and [desArg^{10}]-lysylbradykinin (81), while ACE degrades kinins and desARG kinins by sequential removal of *C*-terminal dipeptides and tripeptides, respectively (82). Although plasma proteases and neutral endopeptidases may also play a role in the metabolism of kinins (9, 24, 25), further assessment of this function in human tissues and biologic fluids is required.

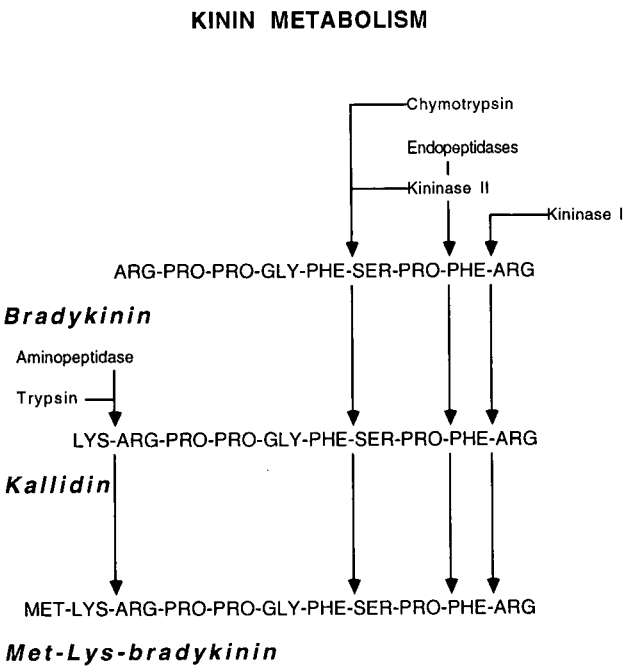

Fig. 1. Kinin degradation pathways.

Activation of the kinin-kallikrein pathway in inflammation

Three different pathways may lead to kinin formation in inflammatory events: a plasma-dependent pathway, a tissue-dependent pathway, and a plasma/tissue-independent pathway (Fig. 2).

Kinin generation in human plasma is dependent upon the interaction of certain negatively charged surfaces with factor XII (Hageman factor – HF) and the circulating prekallikrein-HMWK complex (16, 73, 87). Activated HF (HFA) initiates the conversion of prekallikrein to kallikrein, which, in a positive feedback mechanism, rapidly activates the further conversion of HF in its activated form. Kallikrein has been identified as the major protease capable of activating HF, and it is potentiated in this action by the copresence of HMWK (14). The active kallikrein released by this sequence of events digests HMWK to release bradykinin.

Kinin production within human tissues involves single-chain, acidic glycoproteins known as tissue kallikreins. These enzymes are physicochemically and immunologically distinct from plasma kallikrein, with reported molecular masses ranging from 25 to 43 kDa and isoelectric points close to pH 4 (28, 53). Tissue kallikreins are widely distributed throughout the body tissues in the form of proenzymes, with particularly high levels in the pancreas (56), the kidneys (29), the prostate gland (40), and the lungs (10). Although this indicates a potential for kinin generation at multiple discrete sites, the specific role of kinins at these sites remains to be carefully evaluated. While HMWK serve as the optimal substrate for plasma kallikrein, tissue kallikreins readily release kinins from both HMWK and LMWK, the latter comprising approximately 70% of the total human kininogen pool (55, 62), thus providing these enzymes with a larger pool of available substrate than is available to plasma kallikrein. In many tissues, cleavage of an *N*-terminal peptide converts tissue kallikrein into an active enzyme. Although it is known that prekallikrein can be activated by trypsin, plasmin, or even plasma kallikrein, the identity of such an endogenous, kallikrein-activating system in tissues remains unknown. Activated tissue kallikreins are less susceptible to inhibition by protease inhibitors than is plasma kallikrein (33), and they are the only enzymes known to hydrolyze two dissimilar bonds in LMWK to generate the bradykinin precursor kallidin (86).

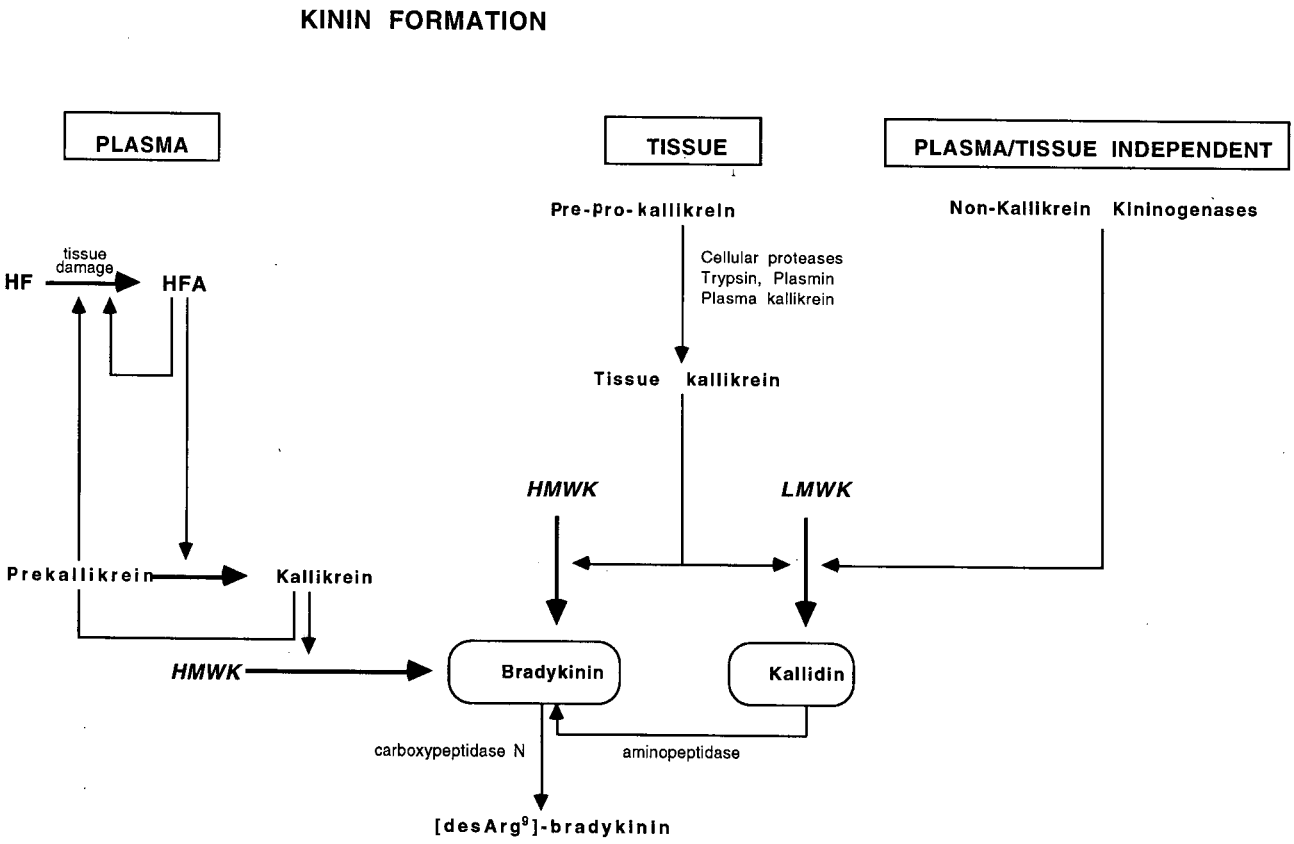

Fig. 2. Schematic flow diagram showing mechanisms of kinin formation by plasma, tissue, and plasma/tissue-independent pathways (see text for details).

The plasma/tissue-independent pathway involves the action of kininogenases other than kallikreins in the cleavage of HMWK and LMWK to form kinins. The ability of a number of inflammatory cell types to liberate proteases which might also display additional kininogenase-like activity has attracted the attention of several investigators. Thus, elastase released from activated neutrophils exhibits kininogenase activity (46). Of relevance to allergic diseases is the observation that both mast cell (63) and basophil (52) proteases display some kininogenase activity *in vitro*. More extensive work is required in this area of research to support the view that this activation pathway may have a significant role *in vivo*.

Kinin receptors classification

Once bradykinin and related kinins are generated, they exert their biologic activities through interaction with two main kinin receptor types, designated B_1 and B_2, on the basis of studies of differing agonist potencies in a number of different tissue preparations (74). In cat ileal preparations (23) and in isolated canine tracheal strips (72), both bradykinin and kallidin selectively activate B_2 receptors, while the B_1 agonist [desArg^9]-bradykinin is without effect. On the rabbit aorta the situation is reversed, with [desArg^9]-bradykinin inducing contraction, whereas bradykinin and kallidin are inactive (75). Recent pharmacologic studies suggest that multiple B_2 kinin receptors may exist (7, 76). Moreover, a so-called B_3 receptor has been described in guinea pig isolated airways and in tracheal smooth-muscle cell culture from the same animal (26, 27). However, characterization of kinin receptors by the simple criteria of the order of potency of agonists and by the use of weak antagonists provides limited information. Only with the availability of specific cDNA probes, and of potent and selective antagonists of kinin receptors will it become possible to discover true differences in kinin receptors subtypes. The distribution of B_2 receptors has been mapped out in human and guinea pig lung by autoradiography with [^{3}H] bradykinin (45), which reveals binding sites in bronchial and pulmonary vessels at the level of endothelial cells. Epithelial cells, airway smooth muscle, submucosal glands, and nerve endings are also labeled. Furthermore, ligand-binding studies with [^{125}I] bradykinin identify the presence of B_2 recep-

tors on vascular and sensory neural sites in the human nose (1). These findings suggest that kinins may have a variety of functions in the lower and upper airways.

The effector function of kinins

Kallikreins and kinins have been shown to reproduce the basic symptoms of inflammation in many animal species, including man (62, 74). Kinins have several potent effects relevant to the pathogenesis of allergic diseases, many of which are mediated via a B_2 receptor.

Kinins elicit prompt vasodilation and are potent inducers of microvascular leakage in many tissues and structures. When injected intradermally in man, both bradykinin and kallidin are potent vasodilators of skin vessels and elicit a dose-related increase in wheal and flare which is not inhibited by either cyclooxygenase inhibition or antihistamine pretreatment (19, 57). These responses are likely to be mediated via the activation of specific B_2 receptors, as [desArg^9]-bradykinin was found to have very limited effect in inducing wheal and flare (57). Additionally, kinins may stimulate sensory nerve endings, thus inducing the local release of potent vasoactive peptides such as substance P (SP), neurokinin A (NKA), and calcitonin gene-related peptide (CGRP) (80). In support of this, pretreatment with topical capsaicin, an irritant which is known to elicit neuropeptide depletion in sensory nerves, greatly attenuates skin responses induced by bradykinin in man (18). Kinins are also potent vasodilators of bronchial vessels and cause an increase in airway blood flow and in microvascular leak (17, 39, 54, 79). The immediate leakage response to bradykinin is partly mediated via the release of platelet-activating factor (PAF) (77) and of neuropeptides from airway sensory nerves (80). The effect of bradykinin on leakage is likely to be mediated via B_2 receptors, which are located on endothelial cells on postcapillary venules because B_2 antagonists inhibit the leakage response (36, 78). In addition, the microvascular leakage induced by bradykinin is increased by inhibition of both neutral endopeptidase and angiotensin-converting enzyme (42).

Collier et al. (15) were the first to demonstrate that bradykinin and its analogs cause a potent contractile response in isolated perfused lungs of guinea pigs and in anesthetized guinea pigs. As a result of these findings, bradykinin was investigated for its *in vitro* and *in vivo* effects on human airways. *In vitro* bradykinin elicits only a weak and variable constrictor response in human airways (6, 83). These responses are influenced by the presence of airway epithelium and by the activity of local degrading enzymes. Bradykinin causes relaxation of intact guinea pig trachea, but constricts airways if epithelium is removed mechanically (7, 31). Bradykinin releases the protective prostaglandin E_2 from epithelial cells (7); removing the epithelium therefore reduces the functional antagonism, resulting in an unopposed constrictor effect of bradykinin. In addition, the enzyme neutral endopeptidase 24.11 is strongly expressed on airway epithelial cells (51); 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 (31). Shedding of the epithelium is commonly observed in asthmatic airways, and this could be a factor contributing to the increased airway response to inhaled kinins in asthma. While inhalation of bradykinin aerosols was shown to have no detectable effect on airway caliber in normal subjects (58, 83), when administered to patients with asthma it resulted in a concentration-related bronchoconstriction (32, 35, 58, 83), thus suggesting an increased responsiveness of airway smooth muscle to kinins, as is observed with other spasmogens. A degree of selectivity for the activation of the B_2 receptor was suggested by the finding that the B_1 receptor agonist, [desArg^9]-bradykinin, had no measurable effect on airway function in either normal or asthmatic subjects (58). In addition, repeated inhalations of bradykinin or kallidin resulted in tachyphylaxis, cross-reactivity occurring between the two peptides (61), thus supporting the view that both bradykinin and kallidin act via the same B_2 receptors. Since no specific and competitive B_2 receptor blockers are yet available for *in vivo* studies in man, conclusive evidence that kinin-induced bronchoconstriction in asthma is due to a specific stimulation of the B_2 receptors cannot be found.

Perhaps the most important property of kinins is their ability to activate C fiber nociceptive sensory nerve endings. Bradykinin is the mediator of inflammatory pain (84), 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 (32). Single fiber recordings from sensory nerves indicate that bradykinin directly stimulates airway C fibers in dogs and guinea pigs (20, 30, 38). The effect of bradykinin on airway sensory nerves is blocked by the potent B_2 antagonist HOE 140 (48). In guinea pigs, a combination of atropine and capsaicin pretreatment largely eliminates the bronchoconstrictor response to instilled bradykinin, indicating that both a cholinergic reflex and release of neuropeptides from sensory nerves play a part (37). In support of this, it has been shown that bradykinin releases tachykinins from perfused guinea pig lung (80).

Relevance of the kallikrein-kinin system in the pathophysiology of asthma

The contractile and edema-promoting properties of kinins suggest that they act as ideal mediators of inflammatory conditions in the lower airways. In airway inflammation it is likely that kinins are formed at the airway surface from plasma kininogens exuded into the airway lumen from leaky superficial blood vessels. However, to implicate kinins in the pathogenesis of asthma, we must satisfy three major criteria. Firstly, kinin generation in association with disease expression must be sought. Secondly, administration of physiologic quantities of kinins to tissue targets must reproduce at least some of the symptoms or physiologic abnormalities of the disease. Thirdly, selective kinin receptor blockade or disruption of the kinin-kallikrein pathway must give rise to some inhibition of those symptoms elicited by exogenously administered kinins.

Evidence that kinin generation may be increased under conditions which prevail in areas of allergic inflammation has been recently obtained from studies in allergic asthmatic (10, 11, 41) and rhinitic airways (50, 67) and in allergic conjunctiva (66) which have demonstrated raised levels of kinins within minutes of local challenge with allergen. In 1987, Christiansen et al. (10) demonstrated kinin levels to be significantly elevated in bronchoalveolar lavage fluids (BALFs) from asthmatics who either had active symptoms of asthma or were responding to aerosolized allergen challenge. Moreover, they showed that increased concentrations of free kinins correlated positively with the detection of augmented levels of tissue kallikrein in BALFs from asthmatic subjects. In the asthmatic airways, the activity of this tissue kallikrein appears to be uneffectively regulated by an α_1-antiproteinase (12). Endobronchial challenge has been used to confirm that allergen exposure of asthmatic subjects results in increased kinin generation (11, 41) and to show that kinin levels are also elevated 19 h after allergen challenge (41). Taken together, these findings indicate that mechanisms for the generation of kinins are active during asthma.

When administered as an aerosol to asthmatic, but not to normal, subjects, kinins provoke bronchoconstriction of rapid onset, the subject then gradually recovering (32, 35, 58, 83). Although in asthmatic airways the bronchoconstrictor effect of bradykinin is likely to be mediated via a B_2 receptor, as the B_1 selective agonist [desArg^9]-bradykinin has no effect on airway function in asthmatic subjects (58), the precise mechanism by which kinins mediate bronchoconstriction in asthmatic subjects is still not clear. Although it has not been possible to administer many of the kinin receptor antagonists to human beings for toxicologic reasons, alternative pharmacologic approaches have been employed. In asthmatic subjects, inhibition of cyclooxygenase by flurbiprofen or aspirin has little or no effect on the bronchoconstrictor effect of inhaled bradykinin (32, 60). Likewise, the mode of action of bradykinin in provoking bronchoconstriction in asthmatic subjects does not seem to involve the release of functionally active histamine (60). There is now accumulating evidence that local neural reflexes may contribute to the contractile airway response to inhaled kinins in asthma. The potent anticholinergic agent, ipratropium bromide, produces an approximately fivefold protection for the airways against bronchoconstriction provoked by bradykinin (32), indicating that cholinergic vagal reflexes may, in part, contribute to this response. Additional support for neuronal involvement in bradykinin-induced bronchoconstriction is gained from the finding that pretreatment with sodium cromoglycate and nedocromil sodium, both considered to have the ability to inhibit peptidergic neural reflexes in addition to their effect on mast cells (13), is very effective in attenuating the airways response to bradykinin challenge in asthmatic subjects (21, 32). It is also possible that at least some of the reported protection afforded against the airways effect of bradykinin by the loop diuretic, frusemide, is due to the ability of this drug to inhibit peptidergic neural reflexes when administered by inhalation in asthmatics (68). Furthermore, a recent study has shown tachyphylaxis after repeated bradykinin challenge which is specific for the nonapeptide and is not secondary to the production of bronchoprotective prostaglandins (59). Capsaicin and bradykinin are thought to stimulate the release and subsequent depletion of sensory neuropeptides from unmyelinated afferent fibers in a variety of animals (Maggi & Meli (44)), thus indicating that neuropeptides release may also be involved in the kinin-induced contractile response. Although these findings indicate C fiber activation with subsequent depletion of neural mediators in kinin-induced asthma, more work in this area of research is necessary to elucidate their mode of action in human asthma.

Relevance of the kallikrein-kinin system in the pathophysiology of rhinitis

Proud et al. (67) were the first to demonstrate that kinins could be generated during allergic inflammation in man, implementing a model of nasal provocation with allergen in which inflammatory mediators could be assayed in secretions recovered by lavage. Kinin formation correlated well with the onset of nasal symptoms and with the increase in nasal lavage fluid of other inflammatory mediators, but was not observed following allergen challenge of

nonallergic subjects. Since these initial observations, increased levels of kinins have now been documented in a variety of inflammatory conditions of the upper airways, including the late-phase allergic response (50), naturally occurring seasonal allergic rhinitis (85), and both experimental and naturally occurring viral infections (49, 64). The nasal model has also lent itself to biochemical studies of the mechanisms of kinin formation and metabolism during the immediate allergic response. High-pressure liquid chromatography (HPLC) analysis of the kinin pool generated during this reaction showed that it consisted of both bradykinin and kallidin (67), thus suggesting that more than one enzyme is involved in kinin formation. During the allergic response, both HMWK and LMWK enter nasal secretions by transudation from plasma (5). Since prekallikrein circulates in plasma as a complex with HMWK, it was not surprising to detect increased levels of plasma kallikrein in nasal secretions during the allergic reaction (3), and their copresence would contribute to the local formation of bradykinin in the nose. However, tissue kallikrein has been shown to cause most of the kininogenase activity in post-allergen-challenge lavage (4) and is unique in its ability to release kallidin, which is found in large quantities in nasal lavage fluids (50, 67).

An additional criterion which must be met to demonstrate a role for kinins in rhinitis is that exogenous kinins should reproduce at least some of the symptoms of the clinical condition. Three studies have recently reported that nasal challenge with kinins mimics many of the symptoms of rhinitis and increases plasma protein leakage in subjects with stable allergic rhinitis and in healthy persons (22, 65, 69). In addition, nasal provocation with bradykinin and kallidin, but not [desArg^9]-bradykinin, elicits many of the symptoms of rhinitis in a dose-dependent fashion, thus suggesting that in man the nasal effect of kinins is mediated via B_2 receptor mechanisms (69). Endogenous kinins may provoke their effects by stimulating B_2 receptors on postcapillary venules and by activating cholinergic and noncholinergic reflex pathways. The nasal effects of bradykinin are uninfluenced by prior pretreatment with the potent H_1-histamine receptor antagonist, terfenadine, or the selective antimuscarinic agent, ipratropium bromide (70), thus indicating that the action of bradykinin within the nose is mediated neither by histamine release nor by reflex cholinergic neurotransmission. As suggested for the lower airways, kinins might cause their effects in the nose by activating specific receptors on afferent nerve endings. As the plasma vascular leakage and nasal congestion induced by bradykinin exposure diminish after repeated capsaicin challenge, it has been suggested that these effects are mediated by local axon reflexes which produce neuropeptide release (43). Unfortunately, it has been difficult to confirm in man these interesting observations (71) which indicate a neat departure from the animal model.

Conclusion

Kinin generation occurs during allergic inflammatory responses, as indicated by its recovery upon allergen exposure, and seems to elicit many of the characteristic symptoms and signs of the allergic disorders, suggesting kinin involvement in disease pathogenesis. However, the relevance of these findings to the pathophysiology of allergic diseases and the mechanism or mechanisms of these effects remain to be defined. The implication of kinins as inflammatory mediators in the pathogenesis of asthma and rhinitis will be conclusively clarified only by potent and specific kinin antagonists that can be used in man; these are now in clinical development. Until that development is complete, it is premature to implicate kinins in the pathogenesis of allergic diseases, and explication of their role must rely on circumstantial evidence.

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