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COMPARATIVE NASAL EFFECTS OF BRADYKININ, KALLIDIN AND [DES-ARG^9]-BRADYKININ IN ATOPIC RHINITIC AND NORMAL VOLUNTEERS

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SUMMARY

1. The structure–activity relationship of kinins within the nose has been investigated in atopic rhinitic ($n = 7$) and non-rhinitic ($n = 7$) subjects. On 4 separate days, each separated by a week, subjects randomly underwent nasal challenge with incremental doses of either the B_1 agonist [Des-Arg^9]-bradykinin, the B_2 agonists kallidin or bradykinin, or vehicle placebo in a double-blind comparative study. The nasal response was monitored objectively by measurement of nasal airways resistance (NAR) by active posterior rhinomanometry and subjectively by symptom reporting of nasal blockage, rhinorrhoea, nasal itch and nasal pain.

2. The B_2 agonists kallidin and bradykinin both induced a dose-dependent increase in NAR ($P < 0{\cdot}001$) and were associated with symptomatic reporting of nasal blockage ($P < 0{\cdot}05$), rhinorrhoea ($P < 0{\cdot}01$) and nasal discomfort ($P < 0{\cdot}05$) compared to placebo. In contrast the effects of the B_1 agonist [Des-Arg^9]-bradykinin on NAR and symptom reporting were indistinguishable from placebo. No difference could be identified in the nasal response to kallidin and bradykinin between rhinitic and non-rhinitic subjects and there was no evidence of B_1 receptor upregulation in the disease state. For the whole group the provocative dose of agonist inducing a 50% increase in NAR (PD_{50}) was $1{\cdot}77 \times 10^{-4}$ mol for bradykinin and $2{\cdot}86 \times 10^{-4}$ mol for kallidin ($P > 0{\cdot}05$).

3. These findings identify that the nasal effects of kinins are mediated through B_2 receptors and the advent of B_2 receptor antagonists will permit a further evaluation of the role of kinins in rhinitis.

INTRODUCTION

Allergic rhinitis is a common condition associated with the symptoms of nasal itch, sneezing, rhinorrhoea and nasal blockage. While the local release of histamine from activated metachromatic cells within the nasal mucosa can explain many of the symptoms (Howarth, 1989) the involvement of non-histamine mediators in this disease is suggested by the incomplete therapeutic effect of H_1 antihistamines,

particularly with respect of nasal blockage (Howarth & Holgate, 1984). Prominent among the non-histamine mediators are the kinins, bradykinin and kallidin (lysylbradykinin), which are potent vasoactive peptides formed as cleavage products from the action of kallikrein on high and low molecular weight kininogens respectively. Increased recovery of these kinins has been identified in nasal secretions from subjects with naturally occurring allergic rhinitis (Svensson, Andersson, Persson, Venge, Alkner & Pipkorn, 1990). In addition Proud, Togias, Naclerio, Crush, Norman & Lichtenstein (1983) have clearly demonstrated that kinins are generated in the nasal mucosa of allergic rhinitic subjects following local allergen challenge. As the release of kinins in nasal lavage fluid is coincidental with the onset of symptoms of rhinitis after local allergen challenge and these kinins are known to exhibit a range of relevant pro-inflammatory actions (Smith, Kage-Sobotka, Bleecker, Traystman, Kaplan, Gralnick, Valentine, Permutt & Lichtenstein, 1980; Dorch, Ring, Reimann & Geiger, 1982; Marceau, Leissier, Regoli & Girroud, 1983) they have been causally implicated in the pathogenesis of allergic rhinitis.

Consistent with the known actions of bradykinin, insufflation of bradykinin into the nose induces nasal blockage, rhinorrhoea and nasal discomfort as well as inducing plasma leakage (Proud, Reynolds, Lacapra, Sobotka, Lichtenstein & Naclerio, 1988). The mechanism(s) for these effects are incompletely understood. As with other autacoids kinins produce their effects by interacting with specific cell surface receptors. Two kinin receptor subtypes are described, B_1 and B_2, based upon studies of differing agonist potencies in separate tissue preparations (Regoli & Barabe, 1980). In the cat ileal preparation (Drouin, St-Pierre & Regoli, 1979) and in isolated canine tracheal strips (Rangachari, McWade & Donoff, 1988) both bradykinin and kallidin, through an action on the B_2 receptors, induce contraction while the B_1 agonist [Des-Arg^9]-bradykinin is without effect. On rabbit aorta the situation is reversed, with [Des-Arg^9]-bradykinin inducing contraction (Regoli & Barabe, 1980) whereas bradykinin and kallidin are inactive. The receptor subtype present within the human nasal mucosa is undefined. This has implications for the specific receptor blockade of the effects of kinins on mucosal surfaces. Furthermore the actions of kallidin and [Des-Arg^9]-bradykinin within the nose are unexplored.

The aim of the present study was to thus investigate the receptor specificity and the comparative potencies of bradykinin, kallidin and [Des-Arg^9]-bradykinin in the nose, monitoring both symptom generation and changes in nasal airways resistance (NAR) as measured by active posterior rhinomanometry. To identify whether disease-specific differences exist these studies have been undertaken in both rhinitic and normal volunteers.

METHODS

Subjects

Seven non-atopic non-rhinitic (five males) and seven atopic rhinitic subjects (four males) participated in the study. They were comparably matched for age, with respective mean ($\pm$S.E.M.) ages of $26{\cdot}2 \pm 1{\cdot}62$ and $31{\cdot}2 \pm 4{\cdot}06$ years. None of the subjects had a history of recent respiratory tract infection, nasal polyps, infective rhinitis, nasal surgery or nasal deformities. None of the rhinitic subjects was taking any form of medication at the time of study and none had received specific immunotherapy within the last 2 years. All of the rhinitic subjects were atopic, as identified by showing positive ($>$ 3 mm wheal diameter) skin prick tests to more than one of the common

inhalant allergens (grass pollens, housedust, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat fur, feathers, nettle, *Candida albicans* and *Aspergillus fumigatus* (Bencard, Brentford, UK)). All seven rhinitics had a history of seasonal rhinitis and their skin tests were compatible with their symptomatology. The other seven volunteers acted as healthy controls, having no history of rhinitis and negative skin prick test responses. All the subjects gave written informed consent and the study was approved by the Southampton hospitals and University joint ethical subcommittee.

Study design

Subjects attended on four occasions at the same time of the day, being randomly allocated to receive nasal challenge with either bradykinin, kallidin, [Des-Arg^9]-bradykinin or vehicle diluent (placebo) in a double-blind cross-over study design. At each visit, separated by at least 1 week, measurements were made of baseline nasal airways resistance (NAR) by active posterior rhinomanometry after 15 min rest. Subjects then underwent nasal challenge with vehicle followed by incremental doses of kinin or placebo at 20 min interval until the top challenge dose had been achieved. After each challenge repeat measurements of NAR were made at 3, 5, 10, 15 and 20 min post-challenge and subjects recorded their nasal symptoms of pruritus, sneezing, rhinorrhoea, pain and nasal blockage on individual rating scales.

Challenge solutions

Bradykinin, kallidin and [Des-Arg^9]-bradykinin (Nova Biochem Ltd, Nottingham, UK) were dissolved in ethanol (10%) and 0·9% sodium chloride to achieve a range of concentrations from $0{\cdot}385 \times 10^{-4}$ to $38{\cdot}5 \times 10^{-4}$ g ml^{-1}. The purity of the synthetic kinins used was confirmed by high-performance liquid chromatography (HPLC) using a solvent system of 1% trifluroacetic acid in water and 1% trifluroacetic acid in acetonitrile after extraction through a C-18 cartridge column (Novapak, Waters, Milford, USA). The bradykinin, kallidin and [Des-Arg^9]-bradykinin eluted as single peaks, as identified by optical density at 210 nm, confirming their purity.

Nasal challenge

In all instances nasal challenge was undertaken bilaterally using a hand-held pump spray delivering 0·13 ml per activation per nostril with a coefficient of variation of output of 8·4%. The spray was placed in one of the nostrils, while occluding the contralateral nostril, and activated once during quiet inspiration. The procedure was then repeated in the opposite nostril. At the concentrations employed this method delivered total doses of kinin, in the 0·26 ml challenge volume, of 20, 200, 1000 and 2000×10^{-6} g equally divided between the two nostrils. These doses were chosen from the previous human studies (Proud *et al.* 1988).

Nasal airways resistance

Total nasal airways resistance was measured before and after each challenge, at the time points indicated, by active posterior rhinomanometry, using a Mercury NR6 Rhinomanometer (Mercury instruments, Glasgow, Scotland). By this method NAR is automatically computed by an on-line microprocessor, from simultaneous measurement of airflow through the nose and the transnasal pressure over four nasal cycles, employing measurement of flow at a constant 75 Pa transnasal pressure differential. For this measurement subjects sit with a clear plastic face mask held, with an airtight seal, over the nose and mouth. The face mask is attached to a pneumotachograph to monitor nasal airflow while breathing quietly through the nose with the mouth closed. The transnasal pressure is derived from measurement of pressure external to the nostrils and from measurement of pressure within the oropharynx through a fine-bore silicone tube placed over the tongue and held through sealed lips. This method of measurement of NAR has a coefficient of variation of repeated measurements of 10·7%.

Symptom recording

All the subjects recorded their symptoms of itching, sneezing, rhinorrhoea, pain and nasal blockage during each 20 min challenge period on separate rating scales. For each period a maximum score of 12 was possibly derived from summation of individual symptom ratings as

detailed: for sneezing, 0 = no sneezes, 1 = < 4 sneezes and 2 = > 4 sneezes; for rhinorrhoea, 0 = absent, 1 = present; for nasal blockage, 0 = not blocked, 1 = single nostril blocked, 2 = both nostrils blocked and 3 = severe bilateral nasal blockage; for pruritus, 0 = absent, 1 = present for each of nose, palate, conjunctivae and inner ear; and for pain, 0 = absent, 1 = present in the nose and pharynx separately.

Data analysis

Baseline NAR values were compared using Wilcoxon's signed-rank test. Changes in NAR in response to the different agonists were expressed as percentage change from the post-diluent values. For each kinin dose the NAR was plotted against the time of measurement to give a series of time–response curves. The response to each agonist was quantified for each dose both as the maximal increase in NAR representing the mean of the 3 and 5 min post-challenge measurements and the area under each time–response curve (AUC) which were calculated by trapezoid integration. For each subject the mean maximum increase in NAR and the AUC were plotted against the dose of the kinin or vehicle on a logarithmic scale and the provocation dose (PD) causing a 50% increase in NAR (PD_{50}) and 800% increase in AUC (PD_{800}AUC) were derived by linear interpolation and geometric mean values calculated for the group. PD values and symptom scores are not assumed to be parametric, therefore comparisons between agonists were made using Friedman's test for multiple matched samples, followed by Student's paired *t* test and Wilcoxon's signed-rank test for paired samples. The nasal response to each agonist was compared as PD_{50} and PD_{800}AUC values using Student's paired *t* test after logarithmic transformation of the data. For each kinin dose symptom scores were summated and compared between agonists using Wilcoxon's signed-rank test. Analyses were carried out for all fourteen subjects and for the rhinitic and normal subjects separately. A probability value $P < 0.05$ was accepted as being significant.

RESULTS

There were no significant differences between the baseline NAR measurements (Pa cm^{-3} s^{-1}) in the rhinitics and non-rhinitics on any of the four challenge days, with group median (range) NAR values for the fourteen subjects on the bradykinin, kallidin, [Des-Arg^9]-bradykinin and vehicle challenge days being 0·138 (0·124–0·146), 0·135 (0·120–0·168), 0·143 (0·126–0·163) and 0·142 (0·121–0·169) respectively ($P > 0.05$).

Both bradykinin and kallidin caused a dose-dependent increase in NAR in the rhinitic and non-rhinitic subjects ($P < 0.001$), while [Des-Arg^9]-bradykinin and vehicle were without significant effect (Figs 1 and 2). There was no significant difference in the effects of bradykinin and kallidin on NAR between the rhinitic and non-rhinitic subjects at any dose level ($P > 0.05$) whether assessed as peak response (Figs 1 and 2) or area under the curve. The mean PD_{50} values for the allergic rhinitic and non-rhinitic subjects for bradykinin (143·4 *vs.* 311·4 μg) and kallidin (343·1 *vs.* 271·2 μg) were not significantly different ($P > 0.05$). The mean PD_{50} bradykinin and PD_{800}AUC bradykinin values calculated from the combined data from the fourteen subjects were 211·5 and 250·1 μg, respectively, which did not significantly differ from the corresponding values with kallidin of 304·6 and 218·8 μg (Table 1). No PD_{50} or PD_{800}AUC could be calculated following nasal challenge with [Des-Arg^9]-bradykinin or vehicle, as no increase in NAR occurred.

Following nasal challenge with vehicle and [Des-Arg^9]-bradykinin no consistent symptoms occurred in any of the fourteen subjects, whereas bradykinin and kallidin caused a dose-related increase in nasal blockage scores in all fourteen subjects (Fig. 3). Nasal blockage was significantly elevated relative to the vehicle and [Des-Arg^9]-

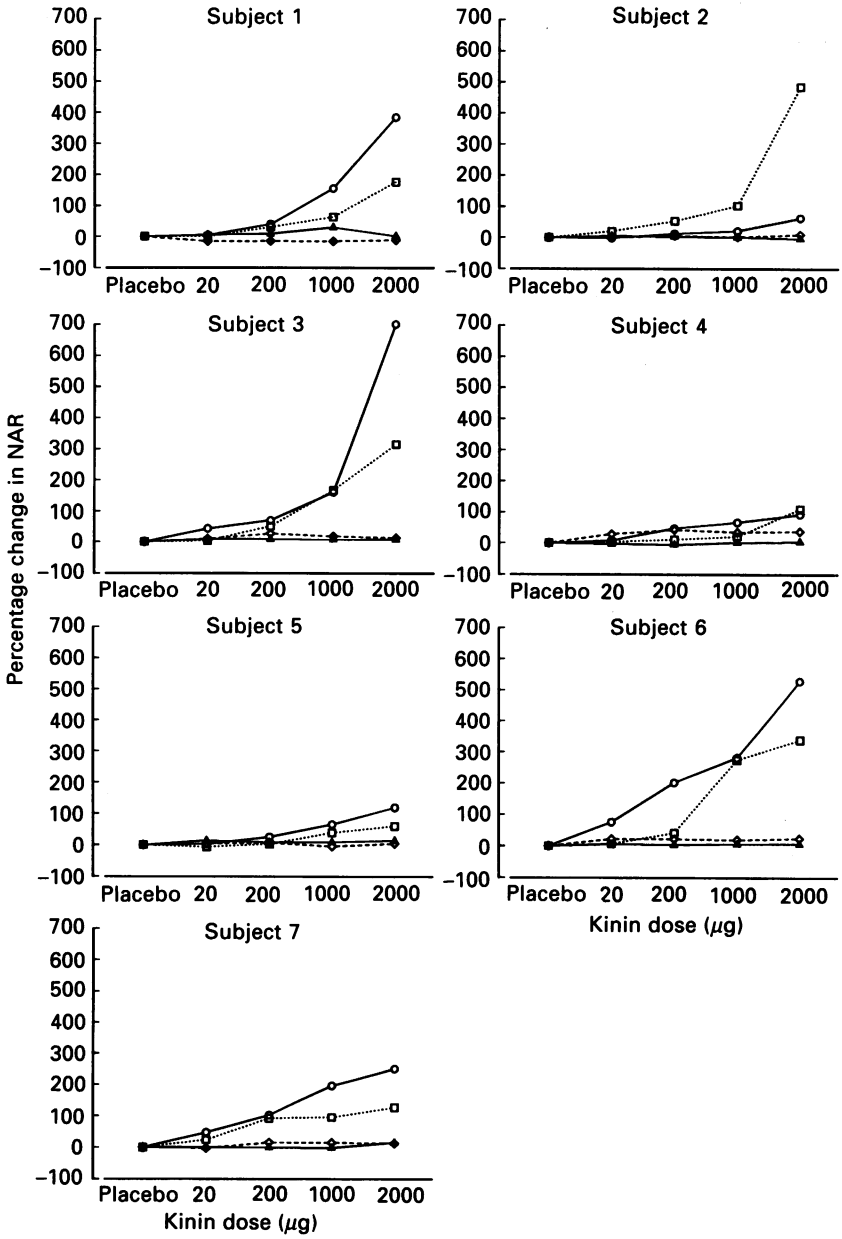

Fig. 1. Individual dose-dependent changes in NAR (percentage change) from post-vehicle baseline for each atopic rhinitic subject (1–7) following nasal challenge with bradykinin (○), kallidin (□), [Des-Arg^9]-bradykinin (▲) and vehicle placebo (◇).

bradykinin challenge days after administration of 20 μg of either bradykinin or kallidin ($P < 0{\cdot}05$). In addition all fourteen subjects reported mild to moderate rhinorrhoea following both bradykinin and kallidin challenge but not with vehicle or [Des-Arg^9]-bradykinin challenge days ($P < 0{\cdot}01$). No difference existed between the

rhinitics or non-rhinitics in their scoring of nasal blockage, or rhinorrhoea. In addition five subjects reported itching in the nose, four sore throat and two pain inside the nostrils after bradykinin and three nasal itching, four sore throat and one pain in the nostrils after kallidin challenge. These effects were not confined to the

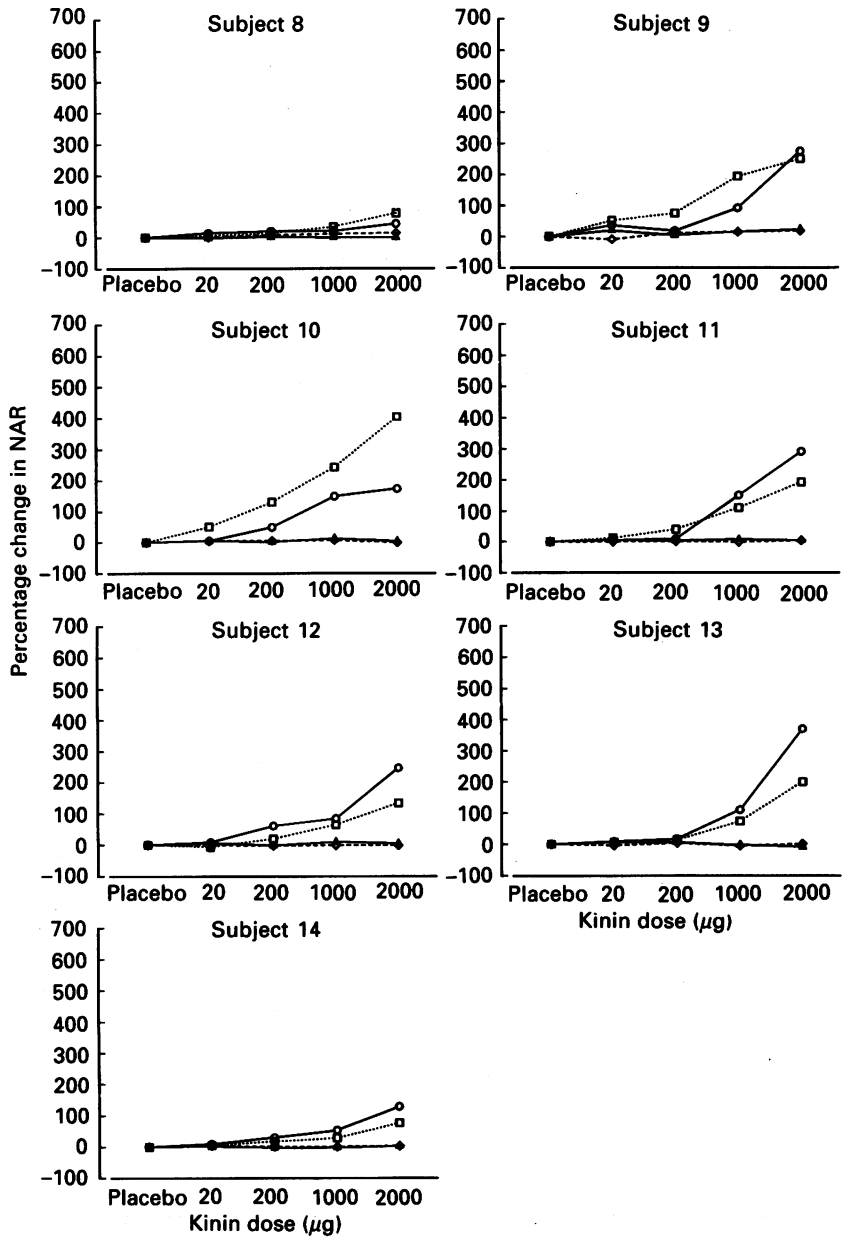

Fig. 2. Individual dose-dependent changes in NAR (percentage change) from post-vehicle baseline for each non-atopic non-rhinitic subject (8–14) following nasal challenge with bradykinin (○), kallidin (□), [Des-Arg^9]-bradykinin (▲) and vehicle placebo (◇).

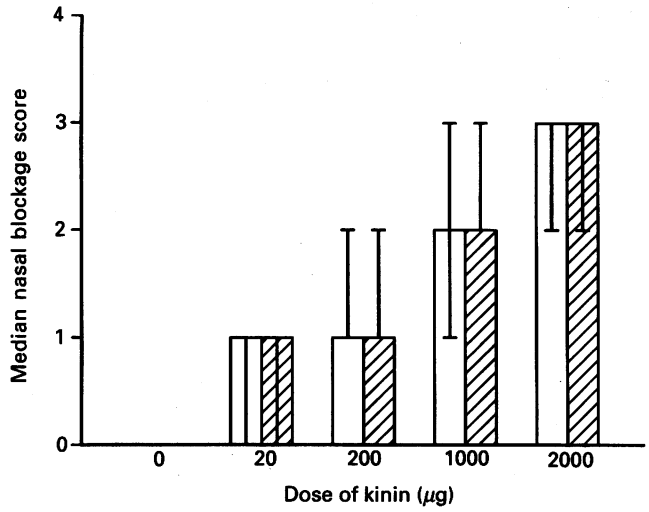

Fig. 3. Median maximal nasal blockage score following nasal challenge with incremental doses of bradykinin (open bar) and kallidin (hatched bar) in fourteen subjects (seven rhinitic, seven non-rhinitic). Vertical lines show range.

TABLE 1. PD_{50} and PD_{800}AUC values for bradykinin (BK) and kallidin (K)

Subject number	PD_{50} BK (μg)	PD_{50} K (μg)	PD_{800}AUC BK (μg)	PD_{800}AUC K (μg)
		Allergic rhinitics		
1	236·7	579·8	66·5	473·3
2	2100·0	167·6	< 20·0	274·8
3	37·2	207·1	860·2	39·9
4	249·3	1428·7	140·3	1805·6
5	616·6	1832·9	1211·9	> 3220·0
6	< 20·0	213·4	21·8	< 20·0
7	21·9	49·5	258·5	1465·9
Geometric mean	143·4	343·1	140·9	366·5
		Normal subjects		
8	> 3220·0	1477·3	3000·0	550·9
9	26·4	21·4	1405·0	< 20·0
10	203·4	20·2	529·3	< 20·0
11	335·0	257·0	40·9	57·8
12	135·8	675·0	413·7	583·8
13	379·3	598·9	264·1	339·5
14	959·5	1639·0	676·2	260·8
Geometric mean	311·4	271·2	489·8	131·0

rhinitic subjects. No subjects sneezed in response to either bradykinin or kallidin challenge.

DISCUSSION

The present study identifies that the kinins, bradykinin (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg) and kallidin (Lys-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg), administered by aerosol to the nasal mucosa, induce rhinorrhoea and a dose-dependent increase in nasal airways resistance. In contrast, the metabolite of bradykinin,

[Des-Arg^9]-bradykinin, is indistinguishable from vehicle placebo in its effects both on nasal airways resistance and nasal symptom reporting. These findings indicate the presence of kinin B_2 receptors but not B_1 receptors within the nasal mucosa. Furthermore comparison between rhinitic and non-rhinitic subjects reveals no disease-related change in either receptor subtype or end-organ sensitivity to these nasally administered kinins.

The comparative dose–response investigation of bradykinin, kallidin and [Des-Arg^9]-bradykinin in the same subjects in this present study has allowed an investigation of the receptor specificity of the nasal responses to these kinins and an assessment of their relative potencies. While previous studies have reported the nasal effects of bradykinin, in inducing nasal blockage, rhinorrhoea and sore throat (Proud *et al.* 1988), no studies have been undertaken with kallidin or [Des-Arg^9]-bradykinin. A number of potential mechanisms for these nasal effects of bradykinin have been proposed, including a non-specific irritant effect. As in the present study the structurally related peptide [Des-Arg^9]-bradykinin (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe), the metabolite of bradykinin, is inactive, a non-specific action is unlikely. The identification that both bradykinin and kallidin but not [Des-Arg^9]-bradykinin induce nasal blockage, as assessed both objectively and subjectively, identifies that this nasal response is mediated through B_2 receptor stimulation. Similarly the constant reporting of anterior rhinorrhoea on the bradykinin and kallidin challenge days, in contrast to the vehicle and [Des-Arg^9]-bradykinin challenges, is consistent with B_2 receptor stimulation mediating this response. These findings with bradykinin and kallidin are in accord with the results from ligand binding studies with ^{125}I-bradykinin which identify bradykinin receptors on the walls of small muscular arteries, arterioles, capillaries, small venules, venous sinusoids and possibly sensorimotor nerve fibres (Baraniuk, Lundgren, Mizoguchi, Peden, Gawin, Merida, Shelhamer & Kaliner, 1990) and indicate that these vascular and neural bradykinin receptors are of the B_2 subtype.

This study represents the first report of the nasal effects of kallidin, the lysine derivative of bradykinin generated from the action of tissue kallikrein on low molecular weight kininogens. Bradykinin and kallidin generation has been reported in patients with symptomatic experimental rhino-virus colds (Naclerio, Proud, Lichtenstein, Sobotka, Hendley, Sorrentino & Gwaltney, 1988) and also in naturally occurring rhinitis (Svennson *et al.* 1990). *In vitro* the effects of bradykinin and kallidin on B_2 receptor-mediated events are similar (Drouin *et al.* 1979; Rangachari *et al.* 1988) and attempts to differentiate their actions by pharmacological manipulation have been unsuccessful (Van Arman & Millar, 1961). In the present study both bradykinin and kallidin induced rhinorrhoea and nasal blockage in all fourteen subjects, with the mean PD_{50} values for nasal blockage for bradykinin and kallidin not being significantly different at 211·5 and 304·6 μg respectively. This is in contrast to the findings from isolated tissue preparations in which higher molecular weight kallidin (molecular weight 1188·0) has been reported to be a more potent B_2 receptor stimulant than bradykinin (molecular weight 1060·2) (Reis, Okio & Rocha E Silva, 1971). However, reanalysis of the present data on a molar basis still identifies the PD_{50} values for bradykinin ($177{\cdot}2 \times 10^{-6}$ mol and kallidin ($286{\cdot}3 \times 10^{-6}$ mol) not to be significantly different. We have chosen PD_{50} as the

provocative dose as all fourteen subjects did not achieve 100% increase in NAR, but all of them achieved 50% increase in NAR which is well outside the coefficient of variation of repeated measurements of 10·7%.

In interpreting these findings consideration must be given to the metabolism of kallidin, as a significant amount of kallidin may be converted to bradykinin by cleavage of the N-terminal lysine residue by aminopeptidase (Regoli & Barabe, 1980). Thus the action of kallidin may be mediated by conversion to bradykinin. While this cannot be excluded in the present study, *in vitro* studies suggest a specific receptor-mediated action of kallidin (Drouin *et al.* 1979; Rangachari *et al.* 1988) and within the confines of the experimental measurements made no difference can be identified between the relative potencies of kallidin and bradykinin on human nasal B_2 receptors.

No nasal effects of the B_1 receptor agonist [Des-Arg^9]-bradykinin have been identified in the present study in either rhinitic or non-rhinitic subjects. This is of relevance as it has been proposed that B_1 receptors may be upregulated in inflammatory disease states (Regoli, Marceau & Barabe, 1978), requiring the presence of immunocompetent cells, possibly tissue macrophages, and the action of interleukin-1 (Deblois, Bouthillier & Marceau, 1988). No such upregulation was apparent in the present study, with [Des-Arg^9]-bradykinin being inactive in both disease and control groups. It is possible that the mild nature of the rhinitics, as suggested by their comparable resting NAR to controls, may overlook a B_1 upregulation in more severe disease but none was identified in these subjects. Furthermore no difference could be found between rhinitics and non-rhinitics in the nasal response to bradykinin and kallidin. The absence of nasal hyper-responsiveness in rhinitics is consistent with a previous report of the effects of nasally administered bradykinin which found no difference in symptom reporting in rhinitic and non-rhinitic subjects (Proud *et al.* 1988). This suggests that there is no vascular hyper-responsiveness to receptor stimulation.

The increase in nasal airways resistance with challenge is vascular, resulting from engorgement of the nasal venous sinusoids secondary to alteration in nasal vascular tone (Howarth, 1989). This vascular effect may be a direct interaction of bradykinin and kallidin on B_2 receptors or indirect, secondary to mast cell degranulation or prostanoid production. Bradykinin has been shown to be a secretagogue for rodent mast cells (Johnson & Erdos, 1973; Deviller, Renoux, Giroud & Regoli, 1985; Ishizaka, Iwata & Ishizaka, 1985) and in dogs to stimulate chloride ion secretion by airway epithelial cells (Davis, Roberts, Coleridge & Coleridge, 1982; Leikauf, Ueki, Nadel & Widdicombe, 1985; Rangachari *et al.* 1988), an effect inhibited by indomethacin (Leikauf *et al.* 1985; Barrow, Dollery, Heavey, Hickling, Ritter & Vial, 1986; Conklin, Burch, Steranka & Axelrod, 1988) suggesting intermediatory production of prostaglandins. An indirect effect is, however, unlikely as nasal challenge with bradykinin, which elicits a dose-dependent increase in NAR, is not associated with increased recovery of nasal lavage histamine (Proud *et al.* 1988) and antihistamines and cyclo-oxygenase-inhibitors do not inhibit bradykinin-induced wheal and flare response in the skin (Crossman & Fuller, 1988) or bradykinin-induced bronchoconstriction (Polosa, Phillips, Lai & Holgate, 1990). Thus the effect of kinins on nasal airflow is likely to represent a direct vascular effect. In contrast the

rhinorrhoea induced by kallidin and bradykinin is likely to be mediated through reflex neuronal activity, consistent with the identification of bradykinin receptors on sensorimotor nerves but not on glands (Baraniuk *et al.* 1990). In support of this, activation of central parasympathetic reflexes have been documented following sensory nerve stimulation with bradykinin in dogs (Davies *et al.* 1982) and stimulation of this reflex pathway with bradykinin has been directly linked to tracheal gland stimulation. The lack of effect of [Des-Arg^9]-bradykinin on rhinorrhoea suggests that this effect is secondary to B_2 receptor stimulation on afferent sensory nerves. In addition to cholinergic reflex mechanisms the rhinorrhoea could be secondary to tachykinin release. In canine and rodent airways bradykinin has been shown to stimulate non-myelinated sensory 'C' fibres and to release substance P and neurokinin A (Geppetti, Maggi, Perretti, Frilli & Manzini, 1988; Saria, Martling, Yan, Theodorsson-Norheim, Gamse & Lundberg, 1988), potential stimulants of glandular secretion. The relevance of this potential pathway within the human nose remains to be fully elucidated. The present study would suggest, however, that these kinin effects are all B_2 receptor mediated.

In conclusion we have shown that bradykinin and kallidin are potent agonists in increasing nasal resistance and in inducing rhinorrhoea as well as nasal discomfort. On the basis of this structure–activity study we have provided evidence for the existence of a B_2 receptor type in the nasal mucosa by showing a different order of potency of kinin analogues that can be accounted for by B_1 and B_2 receptor stimulation. The subsequent availability of potent and selective inhibitors of kinin generation or antagonists of their receptor-mediated effects will enable the further elucidation of the contribution of these mediators to the symptomatology of rhinitis.

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