

Mediators of nasal blockage in allergic rhinitis

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Introduction

Nasal stuffiness is a sensation that arises when there is increased resistance to airflow within the nose. This increased resistance may be related to a fixed obstruction or, as is usual in allergic rhinitis, a variable obstructive event. Examples of fixed obstruction include nasal septal deviation, nasal polyps and malignant tumours. Nasal obstruction in allergic rhinitis that returns to normal, either spontaneously or in response to treatment, is, however, predominantly vascular in nature. Engorgement of the venous sinusoids within the turbinates leads to soft tissue swelling, a reduced internal nasal diameter and increased resistance to airflow. This increase in resistance may be compounded by the presence of intraluminal secretions.

The nasal vasculature and its neural regulation

The nasal submucosa is a richly vascularised tissue, being supplied by the sphenopalatine and anterior ethmoidal arteries. The vascular structure is complex with arterioles beneath the basement membrane feeding subepithelial and glandular capillary networks which empty via cavernous sinusoids into the draining venules. There are also arteriovenous anastomoses diverting blood directly from the arterial to the venous system, and it has been estimated that 60% of the total nasal blood flow is shunted through these arteriovenous anastomoses (1). The superficial capillaries are fenestrated and can allow rapid exudation of protein-rich fluid into the nasal cavity, thereby contributing to nasal secretions. The cavernous sinuses, which compromise a plexus of venous capacitance vessels, are in their densest concentration in the mucosa of the inferior and middle turbinates. Their capacitance volume is under neural regulation with an intrinsic neural tone limiting the sinusoidal capacity. Changes in the venous capacitance volume alter the nasal airflow and nasal airways resistance due to their effect on turbinate size.

In the normal individual the regulation of the venous erectile tissue within the sinusoids, which controls the capacitance system, is primarily autonomic with a prominent sympathetic innervation and less evident parasympathetic supply. The sympathetic neurotransmitters are norepinephrine and neuropeptide Y, and increased sympathetic activity, as occurs with exercise, is associated with constriction of the capacitance vessels and improved nasal airflow. Conversely, loss of sympathetic innervation, as occurs in patients with Horner's syndrome, leads to nasal obstruction on the side of the lesion. Consistent with the relevance of the sympathetic innervation, immunohistochemical studies on nasal tissue have identified the presence of norepinephrine and neuropeptide Y in mucosal nerves (2, 3) and nasal administration of these agents causes vasoconstriction and reduced nasal airway resistance. In contrast, the parasympathetic nervous system in the nose functions as a vasodilator, with acetylcholine, the neuropeptide, vasoactive intestinal polypeptide (VIP) and nitric oxide (NO) as co-transmitters (3, 4). Although acetylcholinesterase, VIP and NO synthase have been co-localised to nasal mucosal nerves, the cholinergic nervous system is only considered to play a relatively minor role in the maintenance of nasal vascular tone as histologic studies have demonstrated a sparse cholinergic innervation around the capacitance vessels (5). In addition to the autonomic regulation, it is now appreciated that non-cholinergic, nonadrenergic neural reflexes are also involved in vascular regulation within the nasal mucosa (6). Activation of sensory neurons, by irritants and locally released inflammatory mediators, has been reported to cause vasodilation and microvascular leakage (4, 6). This is considered to occur both through stimulation of local axonal reflexes and by modification of ganglionic neurotransmission. The neurotransmitters for the axon reflex include the sensory neuropeptides, substance P, neurokinin A, and calcitonin gene-related peptide (CGRP) (2, 3). Activation of the sensory nerves, in addition to stimulating axonal reflexes, influences

neural control of the vasculature via an action on the nerve cell bodies in the trigeminal and sphenopalatine ganglia. These reflexes seem to be mainly vasodilatory, causing nasal blockage through regulation of intrinsic sympathetic tone. Studies undertaken in humans have demonstrated the presence of receptors for substance P, neurokinin A and CGRP in the nasal epithelium, venous blood vessels, arterial blood vessels, glands and neural ganglia of the nasal mucosa (7, 8).

The nasal vasculature is also known to be influenced by a large number of inflammatory and immunologic mediators (9). The action of inflammatory mediators on nasal vasculature is complex. Mediators such as norepinephrine, neuropeptide Y and prostaglandin ($\text{PGF}_2\alpha$) cause vasoconstriction (10). In contrast, mediators such as histamine, bradykinin, PGD_2 , LTC_4 , LTD_4 and platelet activating factor (PAF) are vasodilator agents (10, 11).

Airway inflammation and nasal obstruction

Nasal allergen exposure in subjects with allergic rhinitis is associated with mast cell degranulation and the recruitment of inflammatory cells, in particular eosinophils and basophils. These cell populations, along with epithelial cells, represent the primary effector cells in this disease, with mediator release following their activation inducing the classical nasal symptoms of itch, sneeze, discharge and blockage (12). These symptoms arise following the interaction between released mediators and neural and vascular structures within the nose (13). An understanding of the profile of effect of differing mediators has come from nasal challenge studies. These have identified that histamine, prostaglandin D_2 leukotrienes (LTC_4 , LTD_4), kinins and platelet activating factor, all mediators known to be released in association with allergic reactions, can induce nasal obstruction. In addition, the neural release of substance P from sensory nerves has also been implicated as a potential contributor to naturally occurring nasal obstruction.

Histamine

Histamine is the predominant preformed mediator present within mast cell and basophil granules (13). Immunological activation of mast cells and basophils induces histamine release amounting to 3–5 $\mu\text{g}/10^6$ cells and 1 $\mu\text{g}/10^6$ cells, respectively. This far exceeds the reported ability of both mast cells and basophils to generate leukotrienes such as LTC_4 on immunological activation (each 60 ng/

10^6 cells) and the ability of mast cells to generate prostaglandins such as PGD_2 or platelet activating factor (PAF) (60 ng/ 10^6 cells and 2 pmol/ 10^6 cells, respectively). Thus histamine is quantitatively the major mediator generated on immunological activation of both mast cells and basophils. In the nose, mast cells represent the primary source of histamine (14). Increments in histamine levels in nasal lavage have been identified during both the immediate and late rhinitic responses to topical allergen challenge (14). Although elevated levels have also been reported in naturally occurring disease, this is more difficult to discern, due to its rapid metabolism (15, 16). Elevation of the more stable mediator, tryptase, in nasal lavage does indicate, however, that mast cell degranulation is a feature of both naturally occurring seasonal and perennial allergic rhinitis (17, 18). Nasal challenge with histamine identifies that, in addition to its effects on nasal itch, sneeze and rhinorrhoea, it also contributes to nasal blockage (19). The obstructive effect of histamine is not marked, however, requiring relatively high concentrations and the response being of short duration.

The use of H_1 and H_2 receptor antagonists has identified that while these agents have a partial modifying effect (20), their effect is far from complete in inhibiting histamine-induced nasal obstruction (21). This raises the potential of H_3 -receptor involvement in the nasal obstructive response to histamine. In animal models, H_3 -receptors have been identified in pre-synaptic, perivascular nerve terminals where they modify sympathetic neural transmission (22). Stimulation of H_3 -receptors reduces sympathetic tone and would thus promote engorgement of the venous sinusoids and nasal obstruction. To date there are no H_3 -receptor antagonists for clinical use to verify their involvement in allergic rhinitis.

Prostaglandin D_2

Prostaglandin (PG) D_2 is the predominant prostanoid generated following immunological mast cell degranulation (12, 13). Elevated levels of PGD_2 have been reported in nasal lavage fluid during the immediate nasal response to allergen challenge (14) and, in view of the evidence for on-going mast cell degranulation in naturally occurring disease, this prostanoid is also likely to contribute to the pathogenesis of clinical forms of allergic rhinitis.

Nasal challenge with PGD_2 induces a sustained nasal obstruction (23, 24). This is prevented by the prior administration of the topical vasoconstrictor oxymetazoline, indicative of the vascular nature of the obstructive response. The nasal obstructive response is dose-related (Fig. 1) and comparative

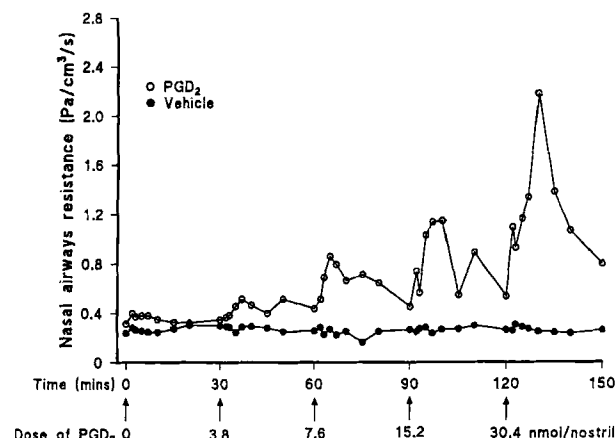


Fig. 1. Influence of prostaglandin D₂ (PGD₂) ○—○ and vehicle ●—● in eight subjects with allergic rhinitis on nasal airways resistance, with incremental doses administered at 30-minute intervals.

studies have suggested that PGD₂ is 10 times as potent as histamine on a molar basis.

The nasal effects of PGD₂ may theoretically be mediated by one of two receptor subtypes, either a common thromboxane/prostanoid receptor (the TP receptor) or a specific PGD₂ receptor (the DP receptor). Within the lower airways the obstructive effects of PGD₂ on airflow are mediated by the TP receptor, which is present in airway smooth muscle. Within the upper airways, however, a potent and selective TP receptor antagonist has been shown to have no effect on PGD₂-induced nasal obstruction (25), suggesting that at this site the obstructive effects are mediated by the vascular DP receptor. Consistent with this, the PGD₂ metabolite, 9 α , 11 β PGF₂, which is at least as potent if not more potent than PGD₂ on human smooth muscle TP receptors, is ineffective in inducing nasal congestions (26).

Leukotriene C₄ and D₄

The sulphidopeptide leukotrienes LTC₄ and LTD₄ are generated from arachidonic acid by the action of 5-lipoxygenase enzymes. These enzymes are present in mast cells, basophils and eosinophils so all these cell populations will contribute to the local generation of leukotrienes within the nose. Indeed activated eosinophils generate increased amounts of leukotrienes due to upregulation of the phospholipase activating protein by cytokines, such as TNF α and IL-1 β . This enzyme is essential for the activation of phospholipase A₂ which is involved in the arachidonic acid cleavage from the phospholipid membrane.

Increased recovery of sulphidopeptide leukotrienes is evident in nasal lavage during both the immediate (27) and late asthmatic reactions (15)

and also in naturally occurring seasonal allergic rhinitis (17,28). Nasal challenge with LTC₄ or LTD₄, which acts on the same LTD₄ receptor, induces an increase in nasal airways resistance and an increase in nasal vascular permeability, consistent with the vascular effects of these mediators, with very little effect on nasal itch or sneeze (29–31). Pharmacological inhibition of the 5-lipoxygenase enzyme abrogates acute allergen-induced nasal obstruction (32, 33) and an LTD₄-receptor antagonist has been reported to modify nasal obstruction in naturally occurring disease (34). Nasal challenge studies suggest that LTC₄ and LTD₄ are at least 10 times as potent as histamine on a molar basis in inducing nasal obstruction and thus of comparable potency as PGD₂.

Platelet activating factor

A further product of phospholipid cleavage from the cell membrane following immunological cell activation is platelet activating factor (PAF). Platelet activating factor is derived from a biologically inactive intermediate, lyso-PAF. This conversion to the active form requires the presence of an acetyl co-enzyme A-dependent acetyltransferase enzyme. Nasal lavage analysis reveals an increase in lyso-PAF-aceter rather than PAF following nasal allergen challenge (35). Thus although PAF nasal challenge induces nasal obstruction in patients with allergic rhinitis (36, 37), this phospholipid metabolite may not contribute significantly in naturally occurring disease as its active conversion appears deficient. Nasal challenge with lyso-PAF is without effect.

Kinins

Kinins are potent vasoactive peptides formed *de novo* in biological fluids and tissues during inflammation (38). They are derived from the α_2 -macroglobulins, high and low molecular weight kininogens, through proteolytic cleavage by kininogenases. While tissue and plasma kallikreins represent the most important kininogenase enzymes, of relevance to allergic inflammation are the non-kallikrein kininogenases. Both mast cell and basophil degranulation is associated with an increase in kininogenase activity and kinin activity increases in nasal lavage in both the early and late nasal responses to allergen challenge. Kinins are also present in increased concentrations in nasal lavage during naturally occurring allergic rhinitis (39). Analysis of the kinin pool has identified the presence of both bradykinin and its precursor kallidin (Lys-bradykinin).

Nasal challenge with both kallidin and brady-

kinin induces nasal obstruction, an increase in plasma protein exudation and rhinorrhoea (40, 41), consequences not identified following nasal challenge with the metabolite of bradykinin (des-Arg⁹)-bradykinin (Fig. 2). As this metabolite acts on bradykinin B₁-receptors whereas both bradykinin and kallidin exert their effects through the bradykinin B₂-receptor, the nasal obstructive effects of kinins within the nose are B₂-receptor mediated. These B₂-receptors are on the nasal vasculature, as ligand binding studies with (¹²⁵I)-bradykinin identify binding to the walls of small muscular arteries, capillaries, small venules and venous sinusoids (42).

No bradykinin B₂-receptor antagonists have been investigated in clinical trials in allergic rhinitis. It is thus difficult to ascertain the relative contribution of kinins to nasal obstruction in naturally occurring disease. Although one comparative study investigating the nasal effects of bradykinin, histamine and PGD₂, identified subjectively that both histamine and PGD₂ had the greatest effects on nasal obstruction (23), an objective study investigating the effects of histamine and bradykinin on a molar basis, rather than on a

weight basis (mg/ml basis), found the reverse (43), with bradykinin being more potent than histamine. Obviously of relevance to such discussions are the relative proportions of histamine and bradykinin generated or released during allergic reactions. Measurement in nasal lavage after allergen challenge reveals comparable release, with mean maximum levels of histamine of 5 mg/ml and of bradykinins of 8 mg/ml (44). Thus until a specific receptor antagonist is investigated in naturally occurring disease, the relative importance of kinins in clinical rhinitis will be hard to discern.

Substance P

Both substance P and calcitonin-gene related peptide (CGRP) are released within 3 minutes of nasal allergen challenge (45), as evidenced by increased recovery of these neuropeptides in nasal lavage. Until specific tachykinin receptors are available, however, it is difficult to assess the contribution of axonal reflexes and neuropeptide release from sensory nerves to nasal allergy. Substance P does, however, have several potentially important effects. Nasal challenge with substance P induces nasal

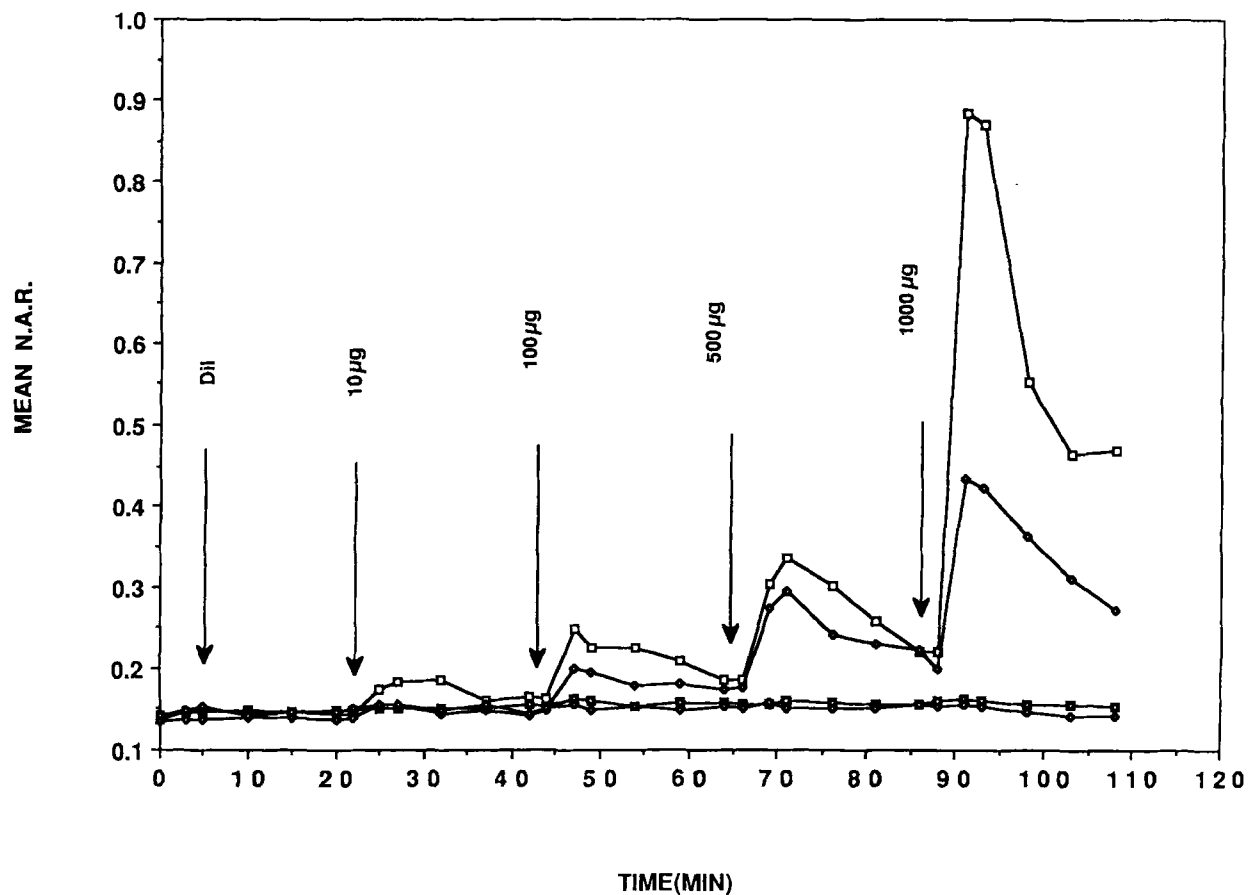


Fig. 2. Influence of bradykinin, kallidin, des-Arg bradykinin and vehicle (mentioned from top to bottom of the figure) on nasal airways resistance (NAR) (Pa/cm³/s) in 14 normal healthy subjects with diluent (Dil) and then incremental doses.

blockage (46) and repeated application of substance P to the nose enhances vascular permeability. Thus substance P could be directly implicated in inducing nasal obstruction. The concentrations of substance P that induce nasal obstruction are, however, associated with noticeable facial flushing, raising the possibility that these nasal effects will only occur at supraphysiological concentrations. Counterbalancing this, is the consideration that the local release of substance P from nerves in close proximity to the nasal vasculature may produce effects at local concentrations considerably less than those evidenced by nasal challenge studies. In addition to these considerations, substance P also has the potential to indirectly influence nasal blockage: it has been shown to induce eosinophil recruitment within the nose (48) and, in human nasal explants, to increase gene expression of cytokines that will prime eosinophils for enhanced activation (49). This effect on gene expression is more marked and more extensive in its profile in nasal tissue from patients with allergic rhinitis than in nasal tissue from healthy controls.

Implications for the management of rhinitis

It is thus apparent that many mediators have the potential to be involved in the nasal obstructive response in allergic rhinitis. It is on account of this duplicity of action that single mediator antagonists have proved poorly efficacious in the amelioration of this disorder. Both H₁-antihistamines and leukotriene receptor antagonists have only partial effects. Specific receptor antagonists for kinins, PGD₂, and PAF as well as SP antagonists have not been clinically assessed. It is probable that their effects would also only be partial, however, due to the unopposed effects of the other mediators.

Nevertheless it is possible that substance P may prove a potentially rewarding target for the following reasons. (a) It is locally released next to blood vessels. (b) It has the potential to modify the nasal vasculature both directly and indirectly, through its effects of eosinophil recruitment and activation. (c) It is likely to be involved not only in allergic disease, as indicated by its release following allergen challenge, but also in non-allergic disease, as repeated capsaicin treatment to the nose, which depletes sensory nerves of their neuropeptides, has been reported to have a long lasting effect in improving symptoms in non allergic rhinitis (50). (d) This neuropeptide will contribute to other features of nasal disease such as mucus production and rhinorrhoea.

Notwithstanding these considerations, however,

it is evident that approaches other than receptor antagonism are needed for the management of nasal blockage in allergic rhinitis. Two approaches are available: either the functional antagonism of the end organ effects of mediators on the nasal vasculature with a vasoconstrictor, such as a topical alpha agonist, or the regular administration of a medication that modifies mucosal inflammation and thus globally diminishes the mediator pool contributing to nasal obstruction, such as a topical corticosteroid. While the former approach is effective in the short term, it is not advocated for long term use on account of the potential for the development of *rhinitis medicamentosa*. The use of regular topical anti-inflammatory therapy is thus the treatment of choice as this therapy will reduce mucosal and epithelial mast cell, basophil and eosinophil recruitment and modify epithelial activation (51). Topical corticosteroid therapy is the most effective single therapy in the long term control of nasal obstruction, being shown to be more efficacious than H₁-antihistamines and topical cromolycate preparations. For topical corticosteroid therapy to be most efficacious, it needs to be taken regularly (52) and is best initiated prophylactically in seasonal allergic rhinitis, as under such circumstances, due to its effects in inhibiting cytokine gene expression, it prevents the seasonal mucosal inflammatory changes and hence the expression of symptoms.

Conclusions

It is apparent that there is at present no single mediator that is responsible for nasal blockage and a broad treatment that reduces inflammation is at present the most effective treatment for chronic therapy. If specific antagonists come forward, it is potentially possible that combination therapies of specific antagonists will also provide a useful alternative but their comparative efficacy to topical corticosteroid therapy in terms both of efficacy and safety would have to be evaluated.

References

1. ÄNGGAARD A. Capillary and shunt blood flow in the nasal mucosa of cats. *Acta Otolaryngol* (Stockh) 1974; 78: 419.
2. UDDMAN R, ÄNGGAARD A, WIDDICOMBE JG. Nerves and neurotransmitters in the nose. In: MYGIND N, PIKORN U, eds. *Allergic and vasomotor rhinitis: pathophysiological aspects*. Copenhagen: Munksgaard, 1987: 50–62.
3. UDDMAN R, SUNDLER F. Innervation of the upper airways. *Clin Chest Med* 1966; 7: 201–9.
4. LUNDBLAD L, SARIA A, LUNDBERG JM, ÄNGGAARD A. Increased vascular permeability in rat nasal mucosa induced by substance P and stimulation of capsaicin sensitive trigeminal neurons. *Acta Otolaryngol* (Stockh) 1983; 96: 479–84.

5. NOMURA Y, MATSUURA T. Distribution and clinical significance of the autonomic nervous system in the human nasal mucosa. *Acta Otolaryngol* (Stockh) 1972; 73: 493-501.
6. LUNDBLAD L, LUNDBERG JM, ÅNGGAARD A. Local and systemic capsaicin pretreatment inhibits sneezing and the increase in nasal vascular permeability induced by certain chemical irritants. *Naunyn Schmiedebergs Arch Pharmacol* 1984; 326: 254-61.
7. BARANIUK JN, LUNDGREN JD, OKAYAMA M, et al. Substance P and neurokinin A (NKA) in human nasal mucosa. *Am J Respir Cell Mol Biol* 1991; 4: 228-36.
8. BARANIUK JN, LUNDGREN JD, GOFF J, et al. Calcitonin gene related peptide (CGRP) in human nasal mucosa. *Am J Physiol* 1990; 258: L81-L8.
9. LUNG MA, PHIPPS RC, WANG JJC, WIDDICOMBE JG. Control of nasal vasculature and airflow resistance in the dog. *J Physiol* 1984; 349: 535-51.
10. HOWARTH PH. Allergic rhinitis: a rational choice of treatment. *Respir Med* 1989; 83: 179-88.
11. RAJAKULASINGAM K, POLOSA R, CHURCH MK, HOLGATE ST, HOWARTH PH. Kinins and rhinitis. *Clin Exp Allergy* 1992; 22: 734-40.
12. HOWARTH PH. The cellular basis for allergic rhinitis. *Allergy* 1995; 50 (Suppl 23): 6-10.
13. HOWARTH PH. Allergic rhinitis: a rational choice of treatment. *Respir Med* 1989; 83: 179-88.
14. NACLERIO RM, PROUD D, TOGIAS AG, et al. Inflammatory mediators in late antigen induced rhinitis. *N Engl J Med* 1985; 313: 65-70.
15. KNANI J, CAMPBELL A, ENANDER I, PETERSON CG, MICHEL FB, BOUSQUET J. Indirect evidence of nasal inflammation assessed by titration of inflammatory mediators and enumeration of cells in nasal secretions of patients with chronic rhinitis. *J Allergy Clin Immunol* 1992; 90: 880-9.
16. BROWN MJ, IND PW, BARNES PJ, JENNER DA, DOLLERY CT. A sensitive and specific radiometric method for the measurement of plasma histamine in normal individuals. *Anal Biochem* 1980; 109: 142-6.
17. KNANI J, CAMPBELL A, ENANDER I, PETERSON CGB, MICHEL FB, BOUSQUET J. Indirect evidence of nasal inflammation assessed by titration of inflammatory mediators and enumeration of cells in nasal secretions of patients with chronic rhinitis. *J Allergy Clin Immunol* 1992; 90: 880-9.
18. RASP G, HOCHSTRASSER K. Trypsin in nasal fluid is a useful marker of allergic rhinitis. *Allergy* 1993; 48: 72-4.
19. MYGIND N, SECHER C, KIRKEGAARD J. Role of histamine and antihistamines in the nose. *Eur J Respir Dis* 1983; 64 (Suppl 128): 16-20.
20. WOOD-BAKER R, LAU L, HOWARTH PH. Histamine and the nasal vasculature: the influence of H₁ and H₂-histamine receptor antagonism on permeability. *Clin Otolaryngol* 1996; 21: 348-52.
21. HAVAS TE, COLE P, PARKER L, OPRYSK D, AYIOMAMITIS A. The effects of combined H₁ and H₂ histamine antagonists on alterations in nasal airflow resistance induced by topical histamine provocation. *J Allergy Clin Immunol* 1986; 78: 856-60.
22. ISHIKAWA S, SPERELAKIS N. A novel class (H₃) of histamine receptors on perivascular nerve termination. *Nature* 1987; 327: 158-60.
23. DOYLE WJ, BOEHM S, SKONER DP. Physiologic responses to intranasal dose-response challenges with histamine, methacholine, bradykinin and prostaglandin in adult volunteers with and without nasal allergy. *J Allergy Clin Immunol* 1990; 86: 924-35.
24. HOWARTH PH, WALSH S, ROBINSON C. Prostaglandin D₂, a mediator of nasal blockage. *J Allergy Clin Immunol* 1990; 85: 223.
25. JOHNSTON SL, SMITH S, HARRISON J, RITTER W, HOWARTH PH. The effect of BAY u3405, a thromboxane receptor antagonist, on prostaglandin D₂-induced nasal blockage. *J Allergy Clin Immunol* 1993; 91: 903-9.
26. HARRISON K, ROBINSON C, BREWSTER H, HOWARTH PH. Comparative effect of prostaglandin D₂, 9 α 11 β PGF and histamine on nasal airflow. Seventh International Conference on Prostaglandins and Related Compounds 1990: 323.
27. CRETICOS PS, PETERS SP, ADKINSON NF JR, et al. Peptide leukotriene release after antigen challenge in patients sensitive to ragweed. *N Engl J Med* 1984; 310: 1626-30.
28. VOLOVITZ B, OSUR SL, BERSTEIN JM, OGRA PL. Leukotriene C₄ release in upper respiratory mucosa during natural exposure to ragweed in ragweed-sensitive children. *J Allergy Clin Immunol* 1988; 82: 414-8.
29. MIADONNA A, TEDESCHI A, LEGGIERI E, et al. Behaviour and clinical relevance of histamine and leukotrienes C₄ and B₄ in grass-pollen-induced rhinitis. *Am Rev Respir Dis* 1987; 136: 357-62.
30. OKUDA M, WATASE T, MEZAWA A, LIU C-M. The role of leukotriene D₄ in allergic rhinitis. *Ann Allergy* 1988; 60: 537-40.
31. BISGAARD H, OLSSON P, BENDE M. Effect of leukotriene D₄ on nasal mucosal blood flow, nasal airways resistance and nasal secretions in humans. *Clin Allergy* 1986; 16: 289-97.
32. KNAPP HR. Reduced allergen-induced nasal congestion and leukotriene synthesis with an orally active 5-lipoxygenase inhibitor. *N Engl J Med* 1990; 327: 1745-8.
33. HOWARTH PH. Lipid mediators and allergic rhinitis. In: ROBINSON C, ed. *Lipid mediators in allergic diseases of the respiratory tract*. Boca Raton: CRC Press, 1993: 109-19.
34. DONNELLY A, GLASS M, MULLER B, et al. Leukotriene D₄ (LTD₄) antagonist ICI 204,219 relieves ragweed allergic rhinitis symptoms. *J Allergy Clin Immunol* 1993; 91: 259.
35. MIADONNA A, TEDESCHI A, ARNOUX B, SALA A, ZANUSSI C, BENVENISTE J. Evidence of PAF-acether metabolic pathway activation in antigen challenge of upper respiratory airways. *Am Rev Respir Dis* 1989; 140: 142-7.
36. LEGGIERI E, TEDESCHI A, LORINI M, BIANCO A, MIADONNA A. Study of the effects of PAF-acether on human nasal airways. *Allergy* 1991; 46: 466-71.
37. PIPKORN U, KARLSSON G, BAKE R. Effect of platelet activating factor on human nasal mucosa. *Allergy* 1984; 39: 141-5.
38. RAJAKULASINGAM K, POLOSA R, CHURCH MK, HOLGATE ST, HOWARTH PH. Kinins and rhinitis. *Clin Exp Allergy* 1992; 22: 734-40.
39. SVENSSON C, ANDERSSON M, PERSSON CGA, VENGE P, ALKNER U, PIPKORN U. Albumin, bradykinin and eosinophil cationic protein on the nasal mucosal surface in patients with hayfever during natural allergen exposure. *J Allergy Clin Immunol* 1990; 85: 828-33.
40. RAJAKULASINGAM K, POLOSA R, HOLGATE ST, HOWARTH PH. Comparative nasal effects of bradykinin, kallidin and (des-Arg⁹) bradykinin in atopic rhinitis and normal volunteers. *J Physiol* 1990; 437: 557-87.
41. RAJAKULASINGAM K, LAU LCK, POLOSA R, CHURCH MK, HOLGATE ST, HOWARTH PH. The temporal relationship between the neural and vascular actions of kallidin within the nose. *Med Inflammation* 1993; 2: 217-23.
42. BARANIUK J, LUNDGREN JD, MIZOGUCHI H, et al. Bradykinin and respiratory mucous membranes. *Am Rev Respir Dis* 1990; 141: 706-14.
43. RAJAKULASINGAM K, POLOSA R, LAU LCK, CHURCH MK, HOLGATE ST, HOWARTH PH. Comparative nasal effects of bradykinin and histamine: influence on nasal airways resistance and plasma protein exudation. *Thorax* 1993; 48: 324-9.
44. PROUD D, TOGIAS A, NACLERIO RM, CRUSH SA, NORMAN

- PS, LICHTENSTEIN LM. Kinins are generated *in vivo* following nasal airway challenge of allergic individuals with allergen. *J Clin Invest* 1983; 72: 1678-85.
45. MOSSIMAN BL, WHITE MV, HOHMAN RJ, GOLOVICH MS, KAULBACH HC, KALINER MA. Substance P, calcitonin-gene related peptide and vasoactive intestinal peptide increase in nasal secretions after allergen challenge in atopic patients. *J Allergy Clin Immunol* 1993; 92: 95-104.
46. DEVILLIER P, DESSANGES JK, RAKATOSIHANAKA JF, et al. Nasal response to substance P and methacholine in subjects with and without allergic rhinitis. *Eur Respir J* 1988; 1: 356-61.
47. BRANNSTEIN G, FAJAC I, LACRONIQUE J, FROSSARD N. Clinical and inflammatory responses to exogenous tachykinins in allergic rhinitis. *Am Rev Respir Dis* 1991; 144: 630-6.
48. FAJAC I, BRAUNSTEIN G, ICKOVIC MR, LACRONIQUE J, FROSSARD N. Selective recruitment of eosinophils by substance P after repeated allergen exposure in allergic rhinitis. *Allergy* 1995; 50: 970-5.
49. OKAMOTO Y, SHIOTORI K, KUDO K, et al. Cytokine expression after the topical administration of substance P to human nasal mucosa: the role of substance P in nasal allergy. *J Immunol* 1993; 151: 4391-8.
50. LACROIX JS, BUVELOT JM, POLLA BS, LUNDBERG JM. Improvement of symptoms of non-allergic chronic rhinitis by local treatment with capsaicin. *Clin Exp Allergy* 1991; 21: 595-600.
51. HOWARTH PH. Glucocorticoids in the treatment of allergic rhinitis: In: SCHLEIMER RP, BUSSE WW, O'BYRNE PM, eds. *Inhaled glucocorticoids in asthma*. New York: Marcel Dekker Inc., 1997: 521-50.
52. JUNIPER EF, GUYATT GH, O'BYRNE PM, VIVEIROS M. Aqueous beclomethasone dipropionate nasal spray: regular versus "as required" use in the treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol* 1990; 86: 380-6.