

The pharmacological basis for the treatment of perennial allergic rhinitis and non-allergic rhinitis with topical corticosteroids

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The currently available respiratory topical corticosteroids are all effective at reducing the nasal symptoms of itch, sneezing, rhinorrhoea and obstruction associated with allergic rhinitis. The mechanism of action of corticosteroids is related to their anti-inflammatory activities. They have been documented to prevent fluid exudation and reduce the number of circulating inflammatory cells, including lymphocytes, mast cells, basophils, eosinophils, macrophages, and neutrophils. This occurs through multiple mechanisms, e.g. eosinophil infiltration is suppressed by preventing cytokine production, reducing local mechanisms of tissue infiltration, and decreasing eosinophil survival. Furthermore, corticosteroids also reduce preformed and newly-generated mediators (e.g. histamine, tryptase, prostanoids, leukotrienes), and inhibit production of cytokines and chemokines by inflammatory cells (e.g. IL-1 through IL-6, IL-8, RANTES, TNF- α , IFN- γ and GM-CSF).

The currently available corticosteroids differ pharmacologically. Fluticasone propionate appears to have the greatest affinity for the glucocorticoid receptor, and binds more quickly and dissociates more slowly from the receptor compared with other corticosteroids, suggesting a more prolonged duration of action. Its increased specificity for respiratory tissue may lead to greater potency with less potential for systemic adverse effects.

Fluticasone propionate has been compared with other corticosteroids in animal models for relative topical and systemic potency, and according to these data, it has the most favourable risk-benefit ratio.

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Mucosal inflammation, characteristic of allergic rhinitis, is associated with the accumulation of inflammatory cells (eosinophils, basophilic cells, lymphocytes, monocytes and neutrophils) in the nasal mucosa, and has been demonstrated in biopsy studies in both seasonal and perennial allergic rhinitis. Consistent with this finding is the associated upregulation of cell adhesion molecules and the local synthesis and release of cytokines and mediators.

Management of allergic rhinitis can be directed at three major stages in the development of the disease. First, attempts can be made to reduce the initiating stimulus, e.g. allergen avoidance. Second, treatment may be targeted towards different aspects of mucosal cell infiltration and activation,

e.g. administration of agents which reduce cell adhesion molecule expression, decrease mediator or cytokine synthesis, or cause receptor inhibition. This is the stage at which corticosteroids have a therapeutic role. Third, treatment may be directed towards end-organs to cause a non-specific reduction in response (e.g. vasoconstriction), or at specific receptors to block the end-organ effects of mediators such as histamine, leukotrienes, or neurotransmitters (e.g. acetylcholine).

Intranasal corticosteroids have been available for the treatment of perennial rhinitis since 1974. They are extremely effective in reducing the nasal symptoms associated with this condition, including sneezing, itching, rhinorrhoea, and nasal obstruction. Although it is important to know which agents

are effective in the treatment of perennial rhinitis, it is also important to understand their mechanisms of action and magnitude of effect in order to use them most appropriately.

Effects of corticosteroids on inflammatory cells

T-lymphocytes

T-lymphocytes play a central role in the allergic response since they recognize antigenic material from antigen-presenting cells, e.g. Langerhans' cells. The subsequent activation of T-lymphocytes and production of cytokines by T-helper cells (TH₂) contribute further to the allergen-induced inflammatory response. It is now known that TH₂ cells produce interleukin-4 (IL-4), and possibly also IL-13, thus promoting immunoglobulin E (IgE) synthesis by B-lymphocytes (1). In addition, the production of IL-3, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF) promotes maturation and activation of eosinophils, and their persistence at allergic tissue sites (2).

In a double-blind, placebo-controlled trial, 48 patients with allergic rhinitis received 6 weeks of treatment with the topical corticosteroid fluticasone propionate 200 µg twice daily or matching placebo, followed by allergen challenge with grass pollen (3). With placebo pretreatment, allergen challenge resulted in T-lymphocyte activation, production of TH₂-type cytokines, and tissue eosinophilia. However, pretreatment with fluticasone propionate significantly inhibited the allergen-induced early (0–60 min) and late (1–24 h) symptomatic responses ($P < 0.05$), with a significant reduction ($P < 0.05$) in T-lymphocytes and the CD4-, CD8- and CD25-positive subsets in the nasal epithelium.

The modest reduction in the number of lymphocytes afforded by corticosteroid therapy is due to induction of "programmed cell death" or apoptosis (4). Topical administration has been shown to inhibit T-lymphocyte activation, prevent increases in IL-4, IL-5 and local IgE and inhibit eosinophil recruitment and activation (5, 6), IL-2 production (7), and IL-2 receptor generation (8).

Eosinophils

Eosinophils are also central to the inflammation and hyperreactivity of airway tissues seen after antigen presentation in sensitized patients. The inflammatory effector capabilities of eosinophils include their capacity to release preformed cytotoxic proteins, such as major basic protein and eosinophil cationic protein (ECP), and granule-associated cytokines (9). Other functions include

the synthesis and release of leukotriene C₄ (LTC₄) (10), and the production of superoxide radicals that are toxic to the respiratory epithelium (11).

Corticosteroids have well recognized effects on the eosinophil component of the inflammatory process by direct induction of eosinophil apoptosis (12) and inhibition of eosinophil recruitment and migration into the nasal airways. Cytokine production in the airways may trigger this cellular infiltration, and inhibition of cytokine production is therefore one of the most important effects of corticosteroid therapy. There are four classes of cytokines that are important in inflammatory cell recruitment – non-specific endothelial activators, cytokines that activate the endothelium specifically, chemokines that directly stimulate cell migration, and cytokines that activate eosinophil function and prolong their survival (13).

Cytokine release after allergen challenge induces the expression of adhesion molecules on endothelial cells (14). Subsequently, the endothelium can actively but non-selectively recruit leukocytes from the circulation, including neutrophils, eosinophils, mononuclear cells, and basophils. Corticosteroids are effective and potent inhibitors of cytokines such as tumour necrosis factor-α (TNF-α) and IL-1, which induce secretion of the non-specific endothelial activators (15). They also inhibit the release of IL-4 and IL-13, thereby preventing expression of specific endothelial cell adhesion molecules, which can bind basophils, eosinophils, monocytes and lymphocytes (5).

Chemokines are cytokines that have chemotactic properties, including the ability to induce cell migration and activate selected cell types. Of particular interest are chemokines that induce eosinophil or lymphocyte migration, such as RANTES and membrane co-factor protein-3 (MCP-3) (16). Corticosteroid treatment has been shown to inhibit the expression of RANTES in airway epithelial cells (17).

The final class of cytokines believed to be important in the allergic response includes IL-3, IL-5, GM-CSF, and interferon-γ (IFN-γ). These cause eosinophil priming and are responsible for the behavioural differences of eosinophils in allergen-sensitized patients compared with normal subjects. This group of cytokines increases adhesion molecule expression, potentiates eosinophil degranulation and movement across an endothelial barrier, and prolongs eosinophil survival (18). Corticosteroids inhibit the production of IL-3, IL-5 and GM-CSF (19), and reduce eosinophil survival time (20).

Thus, corticosteroids have multiple effects on eosinophils – they reduce the number of eosinophils in the circulation, prevent recruitment of

eosinophils to local tissue sites (21), reduce survival of eosinophils, and prevent production of cytokines that are responsible for, or involved in, all of these processes. Indeed, corticosteroids inhibit the production of many cytokines, which may explain much of their anti-inflammatory activity.

Mast cells and basophils

In normal individuals, mast cells are found in the epithelium and lamina propria (22). However, nasal biopsies from symptomatic allergic rhinitis patients have shown an increase in subepithelial and intra-epithelial mast cells, with direct evidence of mast cell degranulation (23). Mast cells and basophils are the only cell types that bear the high-affinity Fcε surface receptor for IgE, and are therefore believed to be the most important cells in IgE-dependent allergic reactions. Mediators released from mast cells following allergenic challenge include histamine, tryptase, leukotrienes (mainly LTC₄) and prostaglandins (mainly PGD₂) (24, 25). Mast cells are also a major source of cytokines, including preformed TNF-α, and IL-4, IL-5, and IL-6, which are newly generated upon mast cell activation (26).

Topical corticosteroids can reduce inflammation by affecting the infiltration of mast cells and basophils. The acute response can be dampened by decreasing the number of mast cells in the nasal mucosa (27–29). Corticosteroid treatment has also been shown to markedly reduce the number of basophils in nasal secretions from allergic rhinitis patients (30). An associated reduction in the release of mast cell mediators has been demonstrated in allergic rhinitis subjects following intranasal corticosteroid treatment, as well as interference with arachidonic acid metabolism and a subsequent decrease in mediator production (31–34). This reduction in the recruitment and activation of eosinophils, basophils and lymphocytes, and the associated decrease in the production of inflammatory mediators, contribute to the value of corticosteroids in relieving the symptoms of allergic rhinitis (35) (Table 1).

Neutrophils

Following allergen challenge, neutrophils are one of the predominant infiltrating cell types in the airway epithelium during the late-phase reaction. These cells are capable of releasing inflammatory mediators, including LTB₄ and platelet-activating factor (PAF).

Corticosteroids are able to inhibit the accumulation of neutrophils (36), possibly due to preventing neutrophil adherence to vascular endothelium by suppressing the release of endothelial-activating

Table 1. Inflammatory mediators in allergic rhinitis and associated symptomatology

Symptom	Mediator
Itching/sneezing	Histamine Prostaglandins
Nasal blockage/microvascular leakage	Histamine Prostaglandins Leukotrienes Platelet-activating factor (PAF) Kinins Chymase Substance P
Mucus secretion	Histamine Eicosanoids PAF Kinins

cytokines, e.g. IL-1, IL-4, and TNF-α, and preventing the release of factors which induce migration through the endothelial barrier, e.g. IL-8, TNF-α, PAF and LTB₄ (37).

Monocytes and macrophages

Monocytes and macrophages are found in abundance and are activated after allergen challenge (38). Corticosteroids reduce the number of tissue macrophages and inhibit their release of IL-1, IFN-γ, TNF-α, and GM-CSF (39).

Table 2 provides an overview of the effects of corticosteroids on all of the affected cell

Table 2. Effects of corticosteroids on inflammatory cells

Cells affected	Corticosteroid effect
T-lymphocytes	Reduction of circulating cell number, apoptosis Inhibition of: T-lymphocyte activation IL-2 production IL-2 receptor generation IL-4 production Antigen-driven proliferation.
Eosinophils	Reduction of circulating cell number, apoptosis Reduction of epithelial and mucosal cell counts Reduction of cell influx in late-phase response Inhibition of IL-4- and IL-5-mediated cell survival
Mast cells/basophils	Reduction of circulating cell counts Reduction of cell influx in late-phase response Reduction of mast cell-derived mediators after challenge Reduction of histamine content and release
Neutrophils	Reduction of cell influx after challenge
Macrophages/monocytes	Reduction of circulating cell counts Inhibition of release of: IL-1 Interferon-γ TNF-α GM-CSF

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populations – T-lymphocytes, eosinophils, mast cells/basophils, neutrophils, and monocytes/macrophages (40).

Epithelial cells

Airway epithelial cells not only act as a barrier but are also effector cells which secrete inflammatory mediators and cytokines, including chemotactic and colony-stimulating factors. Human epithelial cells metabolize arachidonic acid via the cyclo-oxygenase pathway resulting in the production of prostaglandins. Arachidonic acid metabolites, such as leukotrienes, prostaglandins, thromboxane, and PAF, have several activities, including regulation of vascular tone and vascular permeability, stimulation of mucus secretion, chemotaxis, and regulation of cell proliferation. The cytokines produced by epithelial cells can mediate recruitment, activation, and survival of inflammatory cells in the airway.

Corticosteroids interfere with the inflammatory response by blocking the production of arachidonic acid metabolites in many cells. This is accomplished by inducing the production of the anti-inflammatory protein, lipocortin, which inhibits phospholipase A₂, a central enzyme in the arachidonic acid cascade, therefore preventing the generation of cyclo-oxygenase and lipoxygenase products (41, 42).

Blood vessels

Increased blood flow and vascular permeability are important elements of the inflammatory response since they allow transport of plasma proteins and inflammatory cells to the affected site. Many mediators, including histamine, bradykinin, prostaglandins, leukotrienes, and the endothelial-activating cytokines, IL-1 and TNF- α , can contribute to these processes (43, 44).

Topical corticosteroids reduce blood flow and inhibit vascular permeability. The mechanisms for these actions include a reduction in the cyclo-oxygenase metabolites that maintain vascular beds, inhibition of phospholipase A₂, and the subsequent formation of leukotrienes and PAF (45), inhibition of the release of endothelial-derived relaxing factor, production of vasocortin (which reduces permeability), and enhancement of vasospasm by α -adrenergic stimulation (46, 47).

Differences between topical corticosteroids

The onset, duration and magnitude of effect of topical corticosteroids is related to receptor binding capacity, tissue concentration, the susceptibility

of the target tissue, and the pharmacodynamics of the agent.

Receptor binding

Binding to the glucocorticoid receptor is necessary for expression of corticosteroid action, and affinity for the receptor is believed to reflect the potency of the topical agent. Compared with other currently available topical corticosteroids, fluticasone propionate appears to have the strongest affinity for the glucocorticoid receptor in human respiratory tissue (Table 3) (48–50). Furthermore, faster association, a greater degree of binding, and slower dissociation from the receptor may also result in an enhanced effect. Compared with methylprednisolone, dexamethasone, and triamcinolone acetonide, fluticasone propionate has a relatively quicker receptor association (Fig. 1), greater magnitude, and more prolonged receptor binding (51).

Pharmacological effects

Skin blanching activity has been used to compare the topical potencies of corticosteroids, though this method may not be a true reflection of anti-inflammatory potency in the lungs and airways. Using this assay, fluticasone propionate appeared to be the most potent of the respiratory corticosteroids evaluated (52) (Table 3). Furthermore, inhibition of stimulated T-cell proliferation suggests greater anti-inflammatory activity for fluticasone propionate compared with beclomethasone dipropionate and budesonide (53).

The topical to systemic potency ratio, which can be calculated from experimental data, has also been used to compare relative potencies of topical corticosteroids. Inhibition of ear oedema in the rodent (Tonelli test) provides a measure of topical

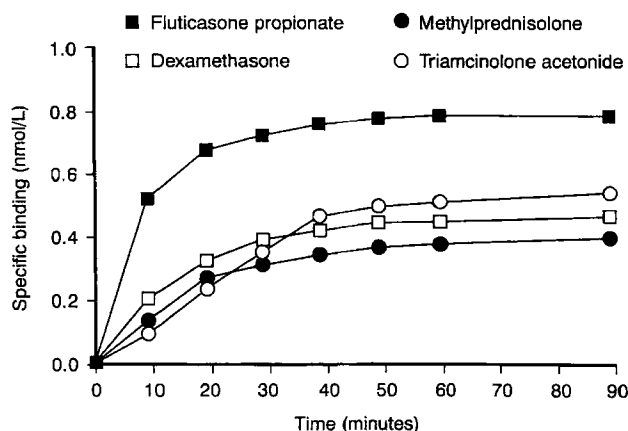


Fig. 1. Rate of association with the glucocorticoid receptor: topical corticosteroids.

Pharmacological basis for corticosteroids in rhinitis

Table 3. Potency of topical corticosteroids based on receptor binding affinity and the skin blanching test

Corticosteroid	Receptor binding affinity*	Skin blanching potency*
Flunisolide	1.8	330
Triamcinolone acetonide	3.6	330
Beclomethasone dipropionate	0.4	600
Budesonide	9.4	980
Fluticasone propionate	18.0	1200

* Relative to dexamethasone (where dexamethasone = 1).

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anti-inflammatory activity, while the degree of thymic involution reflects adverse systemic effects. Fluticasone propionate has been shown to have the most favourable topical to systemic potency ratio when compared with other topical corticosteroids (49, 54) (Table 4).

The efficacy of fluticasone propionate in rhinitis has been shown to be due to its topical activity rather than to any indirect effects following systemic absorption. In a study of over 300 patients with allergic rhinitis, fluticasone propionate aqueous nasal spray 200 µg once daily significantly reduced clinician- and patient-rated symptoms of nasal obstruction, rhinorrhoea, sneezing and itching, compared with placebo or oral fluticasone propionate 5 or 10 mg once daily. The systemic bioavailability of the oral (but not the intranasal) formulation was confirmed in plasma samples (55).

Efficacy studies

Experimental allergen challenge

Following allergen challenge, sensitized individuals immediately develop symptoms of rhinitis, including sneezing, rhinorrhoea, and nasal blockage. However, in approximately 50% of allergic subjects, a late-phase reaction will occur 4–12 h after challenge, with re-occurrence of symptoms. Indeed, symptoms may re-occur even if a lower challenge dose is administered, which is known as the “priming” phenomenon (56).

Nasal lavage immediately after allergen challenge in allergic subjects reveals elevated levels of mucous glycoproteins, histamine, PGD₂, LTC₄, kinin, tryptase, and TAME-esterase. During the late-phase reaction, this response is repeated, except that no increase in tryptase and PGD₂ is evident (57). A large influx of eosinophils, basophils and neutrophils also occurs in the nasal mucosa during the late-phase reaction.

Table 4. Comparison of topical corticosteroids by topical to systemic potency in animal models

Corticosteroid	Topical potency	Systemic potency	Topical : systemic potency ratio
Flunisolide	0.7	12.8	0.05
Triamcinolone acetonide	0.3	5.3	0.05
Beclomethasone dipropionate	0.4	3.5	0.1
Budesonide	1.0	1.0	1.0
Fluticasone propionate	1.7	0.07	25

Pretreatment with topical corticosteroids, even at 48 h prior to allergen challenge, inhibits the acute-phase response in terms of symptom development and mediator release (32, 58). Topical corticosteroids also prevent late-phase symptoms, the late appearance of mediators, and the priming effect. The reduction in mast cell mediators results in part from the decline in mast cell numbers in the nasal mucosa.

Following 2 weeks' treatment with fluticasone propionate 200 µg twice daily, patients with house dust mite allergy were challenged with antigen. Compared with the placebo group, fluticasone propionate treatment significantly reduced the immediate and late-phase symptom scores. The quantity of secretion was significantly diminished in both the immediate and late-phase reactions, and the amount of albumin in the nasal lavage fluid was also reduced. Tryptase release tended to decrease in the acute phase, while ECP release was significantly suppressed in the late phase. Intranasal fluticasone propionate also significantly decreased the non-specific nasal hyperreactivity response to histamine challenge (59).

Clinical studies

A 6-month study compared the therapeutic response of patients with perennial allergic rhinitis treated with fluticasone propionate 100 µg twice daily, 200 µg once daily, or placebo. Total symptom scores (the sum of scores for obstruction, rhinorrhoea, sneezing and itching), as rated by the clinician and patients, were reduced within 1 week of treatment with fluticasone propionate compared with placebo, and this effect was maintained throughout the 6-month treatment period ($P < 0.05$). There were no significant differences in therapeutic response between the groups receiving fluticasone propionate once or twice daily (60).

The efficacy of intranasal corticosteroid treatment for perennial non-allergic rhinitis was evaluated in a 4-week study. Patients ≥ 12 years of age received fluticasone propionate 100 µg or 200 µg or placebo twice daily. The decrease in patient-rated

total nasal symptom scores (the sum of scores for obstruction, rhinorrhoea, post-nasal drainage, and sneezing) was more pronounced with fluticasone propionate 200 µg twice daily compared with placebo on days 15–21 ($P < 0.05$). Patient-rated obstruction improved on days 1–28 with fluticasone propionate 200 µg twice daily and on days 8–28 with fluticasone propionate 100 µg twice daily, compared with placebo ($P < 0.05$) (61).

There have been very few studies examining the efficacy of the available intranasal corticosteroids in head-to-head comparisons. Issues which require consideration include total daily dose, frequency of dosing (once or twice daily), and delivery systems (aqueous or aerosol). These differences make interpretation of the results of available studies difficult, and it is also unclear whether the reported results represent the minimum doses required for symptom control. Data comparing effects on objective parameters of nasal function, outcome with regard to health-related quality of life measures and costs would prove helpful in determining the preferred intranasal corticosteroid. Current data suggest comparable efficacy at the doses studied on a microgram per microgram basis (21).

Tolerability studies

Spontaneous clinical reporting from the many thousands of patients participating in well controlled, double-blind studies of intranasal corticosteroids suggests that the incidence of local drug-related adverse events is not significantly different from placebo, except for a slight increase in reports of small amounts of blood in the nasal mucus. There were no differences in patient reports of systemic adverse effects (21, 60, 61).

At recommended doses, there is no evidence of suppression of the hypothalamic-pituitary-adrenal axis with intranasal corticosteroids (21, 60, 62). Even at four times the recommended dose, intranasal fluticasone propionate 400 µg twice daily for 4 weeks had no effect on adrenal function and response to stimulation using a 6-h cosyntropin infusion test. In this study, oral prednisone (7.5 or 15 mg/day) significantly reduced the response to cosyntropin (63).

Comparisons of oral inhaled corticosteroids suggest that beclomethasone dipropionate, flunisolide, and triamcinolone acetonide are equivalent on a microgram per microgram basis with regard to systemic effects. They appear to have a linear dose-response relationship for suppression of 24 h urine cortisol excretion (64).

In addition, at recommended doses, intranasal corticosteroids do not affect organs sensitive to systemic drug. A 1-year study of adult men with

perennial allergic rhinitis who received either fluticasone propionate 200 µg or placebo once daily, examined possible ocular changes by slit lamp, ocular pressure, and fundoscopic examination. Osteoporosis was also evaluated by bone mineral absorptiometry (DEXA), and blood and urine samples for specific biochemical markers of bone turnover. There were no findings of increased intraocular pressure (>22 mmHg), posterior sub-capsular cataracts, statistically significant changes in bone mineral density in areas of high trabecular bone, in urine levels of pyridinoline or deoxypyridinoline (markers for bone resorption), or serum levels of osteocalcin (marker for bone formation) in either group (65).

Conclusions

These studies, at both the cellular and clinical level, provide evidence to show that the mechanisms of action of topical corticosteroids are related to their anti-inflammatory activities. Anti-inflammatory actions at the cellular level are due to prevention of fluid exudation, reduction of circulating cell numbers, decreased mediator release, interference with arachidonic acid metabolism, thereby causing decreased mediator production, and decreased production of cytokines by inflammatory cells. Clinically, all currently available topical corticosteroids have proved to be effective in reducing the nasal symptoms of allergic rhinitis, but fluticasone propionate appears to have greater affinity for the glucocorticoid receptor, with faster binding and slower dissociation compared with other agents. This would suggest a more prolonged duration of action, while its increased specificity for respiratory tissue may lead to greater potency with less potential for systemic adverse effects. The accumulating knowledge of the mode of action of corticosteroids, combined with clinical experience of good efficacy and tolerability, will allow clinicians to choose the most effective and appropriate treatment for patients with allergic rhinitis.

References

1. Durham SR, Gould HJ, Thienes CP et al. Local control of e-gene expression in B cells of the nasal mucosa in hayfever patients following allergen challenge [Abstract]. *J Allergy Clin Immunol* 1996;97:297.
2. Sims TC, Reece LM, Hilsmeier KA et al. Secretions of chemokines and other cytokines in allergen-induced nasal responses: inhibition by topical steroid treatment. *Am J Respir Crit Care Med* 1995;152:927–33.
3. Rak S, Jacobson MR, Sudderick RM et al. Influence of prolonged treatment with topical corticosteroid (fluticasone propionate) on early and late phase nasal responses and cellular infiltration in the nasal mucosa after allergen challenge. *Clin Exp Allergy* 1994;24:930–9.

4. Cohen JJ. Lymphocyte death induced by glucocorticoids. In: Schleimer RP, Claman HN, Oronsky A, editors. Anti-inflammatory steroid action: basic and clinical aspects. San Diego: Academic Press, 1989:110-31.
5. Masuyama K, Jacobson MR, Rak S et al. Topical glucocorticosteroid (fluticasone propionate) inhibits cells expressing cytokine mRNA for interleukin-4 in the nasal mucosa in allergen-induced rhinitis. *Immunology* 1994;82:192-9.
6. Alvarado C, Reed C, Gleich G et al. Fluticasone propionate aqueous nasal spray reduces nasal eosinophils and cytokine activity of patients with allergic rhinitis [Abstract]. *J Allergy Clin Immunol* 1995;95:193.
7. Schleimer RP. Glucocorticosteroids: their mechanism of action and use in allergic diseases. In: Middleton E, Reed CE, Ellis EF, Adkinson NF, Yunginger JW, editors. Allergy principles and practice. 3rd edition. Washington, DC: Mosby, 1988:739-65.
8. Reed JC, Abidi AH, Alpers JD et al. Effect of cyclosporin A and dexamethasone on interleukin-2 receptor gene expression. *J Immunol* 1986;137:150-4.
9. Wardlaw AJ, Moqbel R, Kay AB. Eosinophils: biology and role in disease. *Adv Immunol* 1995;60:151.
10. Owen WF, Soberman RJ, Yoshimoto T et al. Synthesis and release of leukotriene C₄ by human eosinophils. *J Immunol* 1987;138:532.
11. Zoratti EM, Sedgwick JB, Vrtis RR, Busse WW. The effect of platelet activating factor on the generation of superoxide anion in human eosinophils and neutrophils. *J Allergy Clin Immunol* 1991;88:749.
12. Her E, Frazer J, Austen KF, Owen WF. Eosinophil hemopoietins antagonize the programmed cell death of eosinophils: cytokine and glucocorticoid effects on eosinophils maintained by endothelial cell conditioned medium. *J Clin Invest* 1992;88:1982.
13. Schleimer RP. Effects of glucocorticoids on inflammatory cells relevant to their therapeutic applications in asthma. *Am Rev Respir Dis* 1990;141:S59-69.
14. Bochner BS, Schleimer RP. Endothelial cells and cell adhesion. In: Kaplan AP, editor. Allergy. 2nd edition. Orlando: WB Saunders (in press).
15. Staruch MJ, Wood DD. Reduction of serum interleukin-1-like activity after treatment with dexamethasone. *J Leukoc Biol* 1985;37:193-207.
16. Beck L, Bickel C, Sterbinsky S et al. Injection of human subjects with RANTES causes dermal infiltration of eosinophils (EOS) and mononuclear cells (MNC) [Abstract]. *FASEB J* 1995;9:A804.
17. Stellato C, Beck LA, Gorgone GA et al. Expression of the chemokine RANTES by a human bronchial epithelial cell line: modulation by cytokines and glucocorticoids. *J Immunol* 1995;155:410-8.
18. Warringa RAJ, Loenderman L, Kok PTM et al. Modulation and induction of eosinophil chemotaxis by granulocyte-macrophage colony-stimulating factor and interleukin-3. *Blood* 1991;77:2694-700.
19. Kato M, Schleimer RP. Antiinflammatory steroids inhibit GM-CSF production by human lung tissue. *Lung* 1994;172:113-24.
20. Wallen N, Kita H, Weiler D, Gleich GJ. Glucocorticoids inhibit cytokine-mediated eosinophil survival. *J Immunol* 1991;147:3490-5.
21. van As A, Bronsky EA, Dockhorn RJ et al. Once daily fluticasone propionate is as effective for perennial allergic rhinitis as twice daily beclomethasone dipropionate. *J Allergy Clin Immunol* 1993;91:1146-54.
22. Igarashi Y, Kaliner MA, Hausfeld JN et al. Quantification of resident inflammatory cells in the human nasal mucosa. *J Allergy Clin Immunol* 1993;91:1082-93.
23. Gomez E, Corrado OJ, Baldwin DL et al. Direct *in vivo* evidence for mast cell degranulation during allergen-induced reactions in man. *J Allergy Clin Immunol* 1986;78:637-45.
24. Naclerio RM, Proud D, Togias AG et al. Inflammatory mediators in late antigen-induced rhinitis. *N Engl J Med* 1985;313:65-70.
25. Castells M, Schwartz LB. Tryptase levels in nasal-lavage fluid as an indicator of the immediate allergic response. *J Allergy Clin Immunol* 1988;82:348-55.
26. Bradding P, Roberts JA, Britten KM et al. Interleukin-4, -5, and -6 and tumor necrosis factor- α in normal and asthmatic airways: evidence for the human mast cell as a source of the cytokines. *Am J Respir Cell Mol Biol* 1994;10:471-80.
27. Dahl R, Johansson SA. Importance of duration of treatment with inhaled budesonide on the immediate and late bronchial reaction. *Eur J Respir Dis* 1982;122(Suppl.):167-75.
28. Schleimer RP. The effects of anti-inflammatory steroids on mast cells. In: Kaliner M, Metcalfe D, editors. The mast cell in health and disease. New York: Marcel Dekker, 1992:483.
29. Gomez E, Claque JE, Gatland D, Davis RJ. Effect of topical corticosteroids on seasonally induced increases in nasal mast cells. *Br Med J* 1988;296:1572-3.
30. Bascom R, Wachs M, Naclerio RM et al. Basophil influx occurs after nasal antigen challenge: effects of topical corticosteroid pretreatment. *J Allergy Clin Immunol* 1988;81:580.
31. Blackwell GJ, Carmiccio R, Di Rossa M et al. Macrocortin: a polypeptide causing the antiphospholipase effect of glucocorticoids. *Nature* 1980;287:147-9.
32. Pipkorn U, Proud D, Lichtenstein LM et al. Inhibition of mediator release in allergic rhinitis by pretreatment with topical glucocorticosteroids. *N Engl J Med* 1987;316:1506.
33. Schleimer RP, Lichtenstein LM, Gillespie E. Inhibition of basophil histamine release by antiinflammatory steroids. *Nature* 1981;292:454-5.
34. Meltzer EO, Jalowayski AA, Field EA et al. Intranasal fluticasone propionate reduces histamine and tryptase in the mucosa of allergic rhinitis patients [Abstract]. *J Allergy Clin Immunol* 1993;91:298.
35. Schweibert LA, Beck LA, Stellato C et al. Glucocorticoid inhibition of cytokine production: relevance to antiallergic actions. *J Allergy Clin Immunol* 1996;97:143-52.
36. Bascom R, Pipkorn U, Lichtenstein LM, Naclerio RM. The influx of inflammatory cells into nasal washings during the late response to antigen challenge. *Am Rev Respir Dis* 1988;138:406-12.
37. Bochner B, Rutledge BK, Schleimer RP. Interleukin-1 production by human lung tissue. II. Inhibition by anti-inflammatory steroids. *J Immunol* 1987;39:2303.
38. Fuller RW, Morris PK, Sykes RD et al. Immunoglobulin E-dependent stimulation in human alveolar macrophages: significance in type 1 hypersensitivity. *Clin Exp Immunol* 1986;65:416-26.
39. Guyre PM, Munck A. Glucocorticoid action on monocytes and macrophages. In: Schleimer RP, Claman HN, Oronsky AR, editors. Antiinflammatory steroid action. Basic and clinical aspects. New York: Academic Press, 1991:199-225.
40. Kamada AK, Szeffler SJ. Mechanisms of action of glucocorticoids in asthma and rhinitis. In: Busse WW, Holgate ST, editors. Asthma and rhinitis. Boston: Blackwell Scientific Publications, 1995:1255-66.
41. Flower RJ, Blackwell GJ. Anti-inflammatory steroids induce biosynthesis of a phospholipase A₂ inhibitor which prevents prostaglandin generation. *Nature* 1979;278:456-9.

42. Hirata F, Notsu Y, Iwata M et al. Identification of several species of phospholipase inhibitory protein(s) by radioimmunoassay for lipomodulin. *Biochem Biophys Res Commun* 1982;109:223-30.
43. Larsen GL, Henson PM. Mediators of inflammation. *Annu Rev Immunol* 1983;1:335.
44. Martin S, Maruta K, Burkart V et al. IL-1 and IFN-gamma increase vascular permeability. *Immunology* 1988;64:301.
45. Flower RJ. Lipocortin and the mechanism of action of the glucocorticoids. *Br J Pharmacol* 1988;94:987-1015.
46. Williams TJ, Yarwood H. Effect of glucocorticosteroids on microvascular permeability. *Am Rev Respir Dis* 1990;141:S39.
47. Boschetto P, Rogers DF, Fabbri LM et al. Corticosteroid inhibition of microvascular leakage. *Am Rev Respir Dis* 1991;143:605.
48. Szeffler SJ. Glucocorticoid therapy for asthma: clinical pharmacology. *J Allergy Clin Immunol* 1991;88:147-55.
49. Brattsand R, Axelsson BI. New inhaled glucocorticosteroids. In: Barnes PJ, editor. *New drugs for asthma*. Volume 2. London: IBC Technical Services, 1992:193-208.
50. Barnes PJ. Inhaled glucocorticoids for asthma. *N Engl J Med* 1995;332:868-75.
51. Hogger P, Rohdewald P. Binding kinetics of fluticasone propionate to the human glucocorticoid receptor. *Steroids* 1994;59:597-602.
52. Barnes PJ, Pedersen S. Efficacy and safety of inhaled corticosteroids in asthma. *Am Rev Respir Dis* 1993;148(Suppl.):S1-26.
53. English AF, Neate MS, Quint DJ, Sareen M. Biologic activities of some corticosteroids used in asthma [Abstract]. *Am J Respir Crit Care Med* 1994;149:A212.
54. Brattsand R, Thalen A, Roempke K et al. Development of new glucocorticosteroids with a very high ratio between topical and systemic activities. *Eur J Respir Dis* 1982;122(Suppl.):62-73.
55. Hampel F, Howland W, Martin B et al. The efficacy of fluticasone propionate aqueous nasal spray for treatment of rhinitis is dependent on topical application [Abstract]. *J Allergy Clin Immunol* 1994;93:165.
56. Wachs M, Proud D, Lichtenstein LM et al. Nasal priming. *J Allergy Clin Immunol* 1987;79:253.
57. Naclerio RM, Meier HC, Adkinson NF et al. *In vivo* demonstration of inflammatory mediator release following nasal challenge with antigen. *Eur J Respir Dis* 1983;64(Suppl.):26.
58. Andersson M, Andersson P, Pipkorn U. Topical glucocorticosteroids and allergen-induced increase in nasal reactivity: relationship between treatment time and inhibitory effect. *J Allergy Clin Immunol* 1988;82:1919.
59. Veld CD, Garrelds IM, Jansen APH et al. Effect of intranasal fluticasone propionate on the immediate and late allergic reaction and nasal hyperreactivity in patients with a house dust mite allergy. *Clin Exp Allergy* 1995; 25:966-73.
60. Banov CH, Woehler TR, LaForce CF et al. Once daily intranasal fluticasone propionate is effective for perennial allergic rhinitis. *Ann Allergy* 1994;73:240-6.
61. Selner J, Banov C, Boltansky H et al. Fluticasone propionate aqueous nasal spray effectively treats perennial non-allergic rhinitis [Abstract]. *J Allergy Clin Immunol* 1994;93:165.
62. Brannon MD, Herron JM, Reidenberg P, Affrime MB. Lack of hypothalamic-pituitary-adrenal axis suppression with once-daily or twice-daily beclomethasone dipropionate aqueous nasal spray administered to patients with allergic rhinitis. *Clin Ther* 1995;17:637-47.
63. Vargas R, McMahon FG, Dockhorn R et al. An assessment of HPA axis effects of fluticasone propionate aqueous nasal spray using 6-hour ACTH infusion [Abstract]. *Clin Pharm Ther* 1994;55:184.
64. McCubbin MM, Milavetz G, Grandgeorge S et al. A bioassay for topical and systemic effect of three inhaled corticosteroids. *Clin Pharmacol Ther* 1995;57: 455-60.
65. Li J, Lyles K, Halstenson C et al. Long-term safety study of fluticasone propionate aqueous nasal spray [Abstract]. *Ann Allergy* 1995;74:58.