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THE MECHANISMS OF ANTIINFLAMMATORY STERIOD ACTION IN ALLERGIC DISEASES

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INTRODUCTION

Since the recognition of the antiinflammatory actions of adrenal extracts, the adrenal glucocorticosteroids (hereinafter referred to as steroids) have been the mainstay in the therapy of severe allergic diseases of the skin, the nasal airways, and the lungs. In fact, if their use was not accompanied by undesirable side effects, steroids easily might be the only drugs used. A great deal of progress has been made in our efforts to understand the mechanisms of antiinflammatory steroid action; the purpose of this review is to discuss our present state of knowledge, with an emphasis on steroid actions in the allergic, IgE-mediated diseases. The review has been divided into three major parts: the in vivo actions of steroids, in the clinical setting and in experimental model systems; the in vitro actions of steroids, in particular the effects of steroids on inflammatory cell types likely to be important effectors of allergic disease; and the theories of steroid action, again from the perspective of their antiallergic effects.

THE EFFECTS OF STEROIDS ON IN VIVO MANIFESTATIONS OF ALLERGIC DISEASE

Clinical Findings

This section discusses the antiallergic actions of steroids. The diseases under consideration are broken down into those of the lung, the skin, and the nasal

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airways. I have attempted to discuss the etiology of these diseases in order to put the discussion of steroid action in context.

BRONCHIAL ASTHMA Bronchial asthma is a disease characterized by increased bronchial reactivity, hypertrophy of bronchial smooth muscle, inflammatory cell infiltrate, hypersecretion of mucus, and narrowing of the airways. Its causes are not yet clear. In about one-third of the cases in North America, the disease is clearly IgE/allergen-mediated (extrinsic asthma); in one-third of the cases it has an allergic component; and in one-third (intrinsic asthma) the etiology is not known. Studies done in the early 1950s by Carryer, Cooke, and others demonstrated the effectiveness of ACTH and cortisone against both intrinsic and extrinsic forms of asthma (1–3). The steroid effect required between several hours and several days to be fully expressed (2, 4) (Figure 1). The airway obstruction in chronic asthma is also associated with a loss of elastic recoil, resulting in hyperinflation of the chest; all of these symptoms are reversed with steroid therapy (5). The relatively recent introduction of inhaled steroid preparations, such as beclomethasone dipropionate aerosol, has provided an effective alternative to systemic steroids, with fewer systemic side effects (6).

One characteristic that sets asthmatic patients apart from normal people is a hyperreactivity of the airways to irritant chemicals such as ozone and sulphur dioxide, as well as to exogenously applied mediators such as histamine, methacholine, and prostaglandin F_2. Thus, while these agents cause little or no decrease in airway function in normals, even at high concentrations, asthmatic

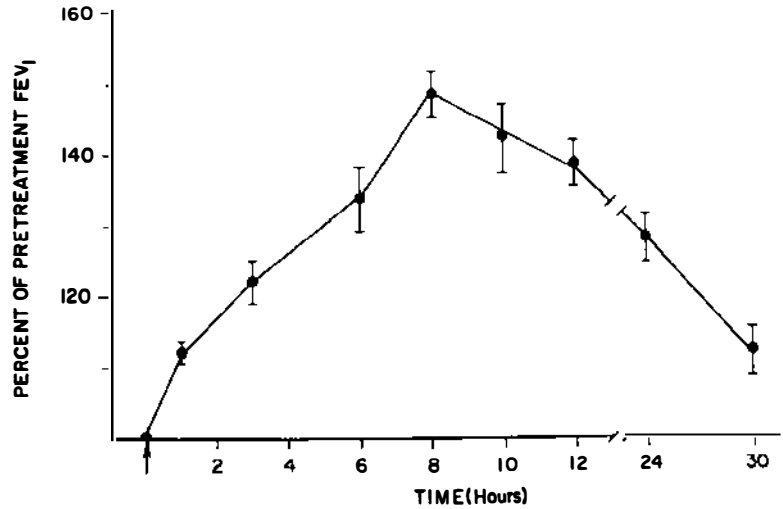

Figure 1 Improvement of airway function in asthmatics receiving a single 40 mg injection of prednisone phosphate [taken from (4)].

subjects experience a marked decrease in airflow following inhalation or parenteral challenge (7, 8). Hargreave and his colleagues have suggested that the sensitivity of asthmatic patients to the airway-constricting effects of methacholine and histamine parallels the severity of their disease (8). It is not yet clear whether this bronchial hyperreactivity is a cause, or merely a symptom, of the disease. Studies indicate that hyperreactivity may be the result of prior exposure to antigen (9), to increased permeability of bronchial epithelium (10), or to local inflammation involving influx of neutrophils (11). Although Arkins et al have claimed that steroid therapy does not reduce asthmatic bronchial hyperreactivity (12), the increase of hyperreactivity following antigen challenge appears to be blocked by steroids (9).

In many severe asthmatic patients, strenuous exercise produces what has been called exercise-induced asthma by an as-yet undetermined mechanism. In contrast to the cases of allergic or intrinsic asthma, steroid therapy, either by inhalation or orally, is only marginally effective against exercise-induced asthma (13–15).

Allergic asthma has been thought for many years to be due to the union of the inhaled allergen with specific IgE on the surface of the pulmonary mast cells, followed by the release of mast-cell inflammatory mediators such as histamine and leukotrienes. The bronchospasm and hypersecretion seen are thought to be due to the action of these mediators. Recent work by Hogg and his associates reconciles this concept with the fact that the bulk of the pulmonary mast cells reside beneath the epithelial barrier, which is impermeable to most allergens. They have proposed that the release of mediators by the small number of superepithelial and interepithelial mast cells is sufficient to increase epithelial permeability so as to allow the allergen access to the large number of subepithelial mast cells (Figure 2)(10). Pare & Hogg have proposed that steroid therapy may block this permeability increase (10).

ALLERGIC DISEASES OF THE SKIN At the same time that steroids were found to be effective antiasthmatic drugs, researchers were establishing their effectiveness against many other immunologically based diseases, including diseases of the skin such as atopic dermatitis, pemphigus vulgaris, and cutaneous-contact hypersensitivity (16–18). Although the etiology of atopic dermatitis is unclear, an IgE-dependent mechanism is suspected. There is a strong correlation between the severity of the disease and serum IgE levels (19). Furthermore, a marked (approximately sevenfold) elevation of Fc_ϵ receptor–positive lymphocytes is seen in these patients. Steroid therapy reduces the number of Fc_ϵ receptor–positive lymphocytes in these patients to the normal range (approximately 1%) (20). Although steroids are effective in the therapy of atopic skin diseases, they do not affect the immediate allergic skin test wheal and flare

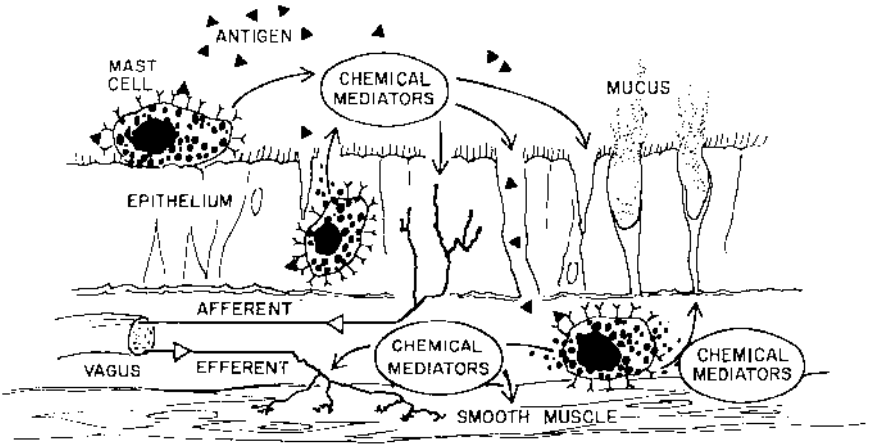

Figure 2 Immediate response to antigen inhalation. Mast cells on the epithelial surface release mediators that increase epithelial permeability and allow the access of antigen to subepithelial mast cells. Degranulation of subepithelial mast cells stimulates smooth muscle contraction and mucus secretion [modified from (10)].

response (2, 3, 21, 22). These paradoxical findings may be reconciled by recognition of the importance of the late cutaneous response (see below).

ALLERGIC RHINITIS Steroid therapy effectively alleviates the symptoms of allergic rhinitis, commonly known as hay fever (21, 23). However, the disease is rarely severe enough to justify systemic steroid therapy and its associated side effects. While the early success of intranasally applied steroids may have been related to systemic absorption of the drugs (24–26), steroids are now available that clearly act locally, without causing any of the systemic side effects, such as adrenal suppression (Figure 3) (27).

Clinical Research

The administration of antigens, or inflammation-provoking substances, can produce reactions that in many ways resemble the naturally occurring allergic diseases. In this section, discussion will focus on such in vivo experimental models, their relevance to particular allergic diseases, and their use as models for the study of steroid action.

THE LATE-PHASE REACTION In atopic subjects, the administration of allergen produces an immediate, vigorous, IgE-dependent response that varies according to the site of administration (bronchospasm in the lungs, wheal and flare in the skin, and sneezing and rhinorrhea in the nose). In a subset of these subjects, the response reappears four to ten hours after the administration of the

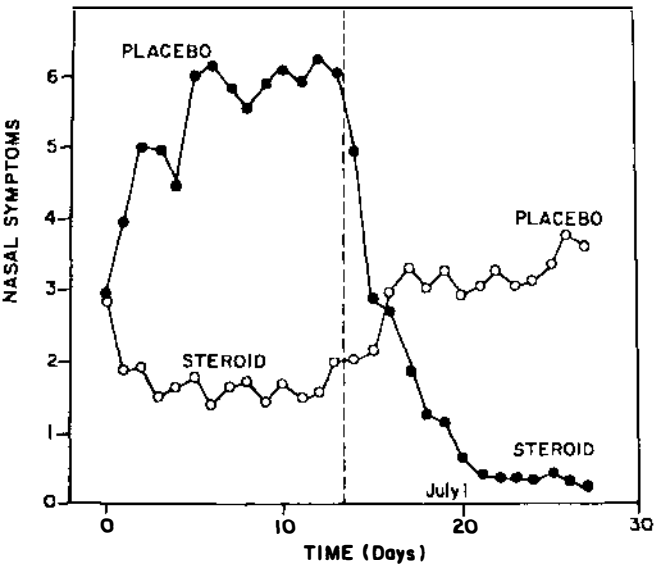

Figure 3 Double-blind cross-over trial of intranasal beclomethasone dipropionate aerosol in hay fever. Placebo and steroid (400 μg daily) groups were switched at the time indicated by the dashed line [adapted from (22)].

allergen in what has been termed the late-phase reaction [elegantly reviewed by Gleich in (28)]. This reaction can also be produced by compound 48/80, a polyamine that causes mast-cell degranulation, and in the rat by a 1400 molecular–weight (MW) component of mast-cell granules (29–31). There is additional evidence that the late-phase reaction (LPR) occurs as a consequence of mast-cell degranulation. The size of the LPR correlates with the size of the preceding immediate reaction to antigen (31, 32). Furthermore, the LPR is clearly IgE-mediated, based on studies that show that it can be produced by specific anti-IgE antibody (22, 33), and it can be passively transferred in skin with purified, antigen-specific IgE antibody (34). While mast-cell degranulation may be necessary to produce an LPR, it may not be sufficient. This hypothesis is based on the studies of Dolovich et al, who showed a minimal LPR in the skin following challenge with codeine (35).

The LPR reflects to a large extent the significant infiltration of inflammatory cells from the blood into the site of allergen administration (see below). Treatment of subjects with steroids prevents the occurrence of the LPR in the lungs, the skin, and the nose (Figure 4) (22, 36–38). Owing to the lack of effect of steroids in inhibiting the immediate response in these models, their effectiveness against the LPR, and their effectiveness in allergic disease, Gleich has suggested that the LPR may be a better model of allergic diseases than the immediate allergic response (28).

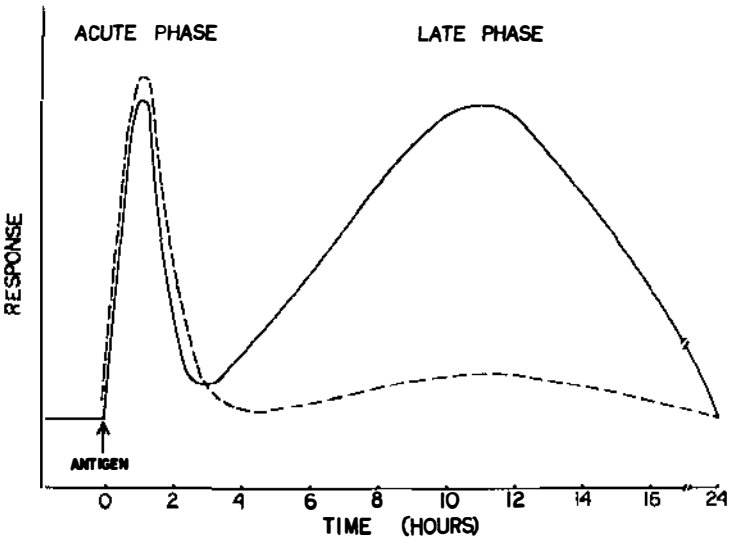

Figure 4 Action of steroids against experimental allergen challenge. Allergen challenge is characterized by an immediate and late-phase response in the skin, the nose, and the airway (solid line). Steroid treatment selectively blocks the late response (dashed line).

BRONCHIAL PROVOCATION As mentioned above, challenging allergic subjects produces a biphasic response characterized by a reduction in lung function (e.g. decreased peak expiratory flow and forced-expiratory volume). Most (33, 36, 39–42), but not all (43–45), investigators find no effect of steroid therapy on the immediate response; the LPR is consistently inhibited by steroid treatment in these studies. Bronchial biopsies of asthma patients have shown that, during a naturally occurring episode of asthma, the number of pulmonary mast cells falls approximately 70%, perhaps indicating in vivo degranulation (46). Salvato claimed that therapy with 3–5 mg of dexamethasone per day reduces the number of mast cells in the bronchial biopsies (46). However, in autopsies of patients who died of acute asthma, Connell demonstrated a marked reduction of tissue mast cells (47). Of the twelve patients in Connell's study, the three who had been on steroid therapy had higher numbers of tissue mast cells than the remaining nine.

During an asthmatic episode, marked changes in the mucociliary apparatus occur. Challenge with ragweed allergen produces a significant decrease in the velocity of tracheal mucociliary transport, which may result from the release of leukotrienes in the airways (see below) (48). Large exudation of mucus into the airways is a marked pathological feature of asthma (47). In vitro studies with human airway tissue by Marom and coworkers indicate that mucus secretion is stimulated by sulfidopeptide leukotrienes and that treatment with dexamethasone in vitro can inhibit the secretion of mucus (Figure 2) (49, 50).

Much emphasis has been placed on identifying the chemical mediator(s) responsible for constricting the airways following bronchial challenge. Unfortunately, many of the likely mediators (histamine, leukotrienes, platelet-activating factor) have such a rapid half-life that their detection in the blood following challenge in the lungs is difficult. Thus far, bronchial-challenge studies have demonstrated a rise in blood histamine and platelet factor four and a high molecular–weight factor chemotactic for neutrophils that is presumably mast cell–derived (44, 51, 52). Serum neutrophil chemotactic factor levels have been seen to rise during both the immediate and the late-phase responses (52).

Leukotrienes Leukotrienes C_4, D_4, and E_4 are sulfidopeptide derivatives of arachidonic acid that are potent constrictors of bronchiolar smooth muscle, both in vitro and in vivo (53–56). These compounds, formerly known as slow-reacting substance of anaphylaxis (SRS-A), are from 600–10,000 times as potent as histamine in causing contraction of isolated human bronchi and in reducing lung function (peak expiratory flow) in normal subjects (55, 56). Since large quantities of leukotrienes are produced by mast cells, basophils, and other inflammatory cells, as well as by isolated lung tissue challenged with antigen, the leukotrienes figure prominently as important potential mediators of asthma (see below). Leukotriene B_4, a dihydroxy derivative of arachidonic acid that lacks the sulfidopeptide moiety, has been found in elevated concentrations in the sputa of asthmatic patients (57). The effects of steroids on leukotriene formation are discussed below.

THE ALLERGEN CHALLENGE OF THE SKIN Studies of the skin have mostly employed one of three techniques: allergen challenge followed by tissue biopsy; denudement of a surface of skin, followed by challenge and then a coverslip cover (the skin window) that is later removed in order to classify and enumerate the cells adhering to it; and skin blister techniques, in which a blister provides an in vivo chamber for the study of mediators and cells. Challenge with allergen produces a cellular infiltrate that is similar in all of these model systems. Polymorphonuclear leukocyte (PMN) infiltration (approximately 4–8 hours) is followed by the influx of eosinophils and basophils; after approximately 24 hours the infiltrate becomes largely mononuclear (lymphocytes, monocytes, and macrophages) (58–61). During the first four hours following allergen, the number of identifiable mast cells decreases, suggesting that mast-cell degranulation has occurred (62). This conclusion is supported by the finding that the mast-cell mediators histamine and PgD_2 appear in skin-blister fluid following allergen challenge (63). The chemotaxis of PMN, eosinophils, basophils, and other agents into the tissue may be stimulated by mast cell–derived, large molecular–weight, specific chemotactic factors that remain to be

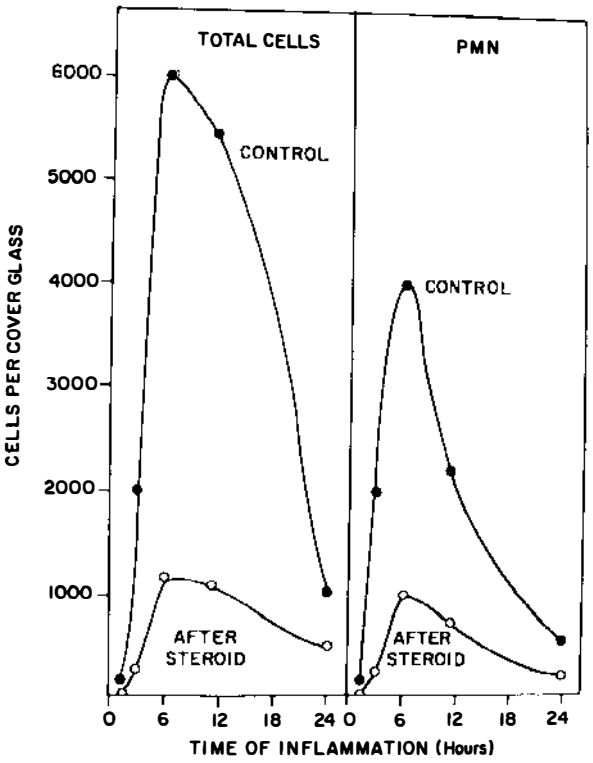

Figure 5 Steroid inhibition of the cellular infiltrate during inflammation, using the skin-window technique [taken from (75a)].

fully characterized, as well as by compounds such as LTB_4 and PgD_2, which can, especially in combination, cause an intense PMN infiltrate in human skin (64) (see below).

As noted earlier, the induration and erythema of the cutaneous late-phase reaction to antigen are inhibited by prior steriod therapy. Most (2, 3, 16, 21, 22, 65–70), but not all (71), investigators find no effect of steroid therapy on the immediate cutaneous (wheal and flare) reaction. A prominent histological feature of steroid action on the late cutaneous response to antigen is an inhibition of the influx of all leukocyte types (PMN, eosinophils, basophils, mononuclear cells, lymphocytes) into the tissue (70, 72–75) (Figure 5). This is one of the most important antiinflammatory actions of the steroids, and it probably occurs by an interference with the adherence of the cells to vascular endothelium prior to their emigration from the circulation into the tissue (see below).

NASAL CHALLENGE Studies of nasal challenge have been hampered by the lack of a reliable, objective criterion by which to judge the action of the

allergen. The major physiological changes are sneezing and the obstruction of nasal airways. The latter can be measured as an increase in nasal-airway resistance (NAR); however, NAR changes occur on a cyclical basis in unchallenged subjects, making baseline values somewhat unreliable. Topical steroid therapy has been reported to cause either a reduction (76, 77) or no change (37, 78) in the allergen-induced increase in nasal-airway resistance. Pipkorn has reported a decrease in the histamine content of nasal mucosa following topical steroids and has concluded that this is due to a reduction in mast-cell histamine content rather than to a decrease in mast-cell numbers (79, 80). Steroid therapy has been reported to reduce the number of eosinophils in nasal smears and the number of mast cells in nasal scrapings (81, 82). Okuda & Mygind have suggested that steroids may reduce the allergen-induced increases in endothelial/epithelial permeability that occur in rhinitis patients (83). Recently, Naclerio et al have developed a nasal-challenge model that allows for the measurement of chemical mediators following allergen challenge (84, 85). Following allergen challenge, histamine, PgD_2, kinins, leukotrienes, and other mediators have been demonstrated in the nasal secretions (84–87). This model system should allow for an objective study of the action of steroids in vivo against experimental allergic rhinitis.

STEROID EFFECTS ON WHITE BLOOD CELLS The administration of steroid orally or parenterally causes significant changes in the circulating white blood–cell profile. Data in Figure 6 summarize the reported effects of a medium dose (e.g. 50 mg prednisone or 350 mg hydrocortisone) of steroid on leukocyte numbers. About 4–8 hours (depending on route of administration) following steroid administration, PMN levels rise to roughly twice resting levels, while the numbers of lymphocytes, monocytes, eosinophils, and basophils fall by approximately 80% (88–92) (Figure 6). Since PMN are the predominant white blood–cell type, total white counts rise slightly or do not change.

The increase in PMN counts reflects an increase of the half-life of the PMN from 7–10 hours, as well as an increase in the circulating, marginal, and therefore total blood-granulocyte pool (93). Studies with radiolabeled lymphocytes by Fauci & Dale indicate that the steroid selectively depletes the recirculating lymphocyte population (94). Further, lymphocyte marker studies indicate that T_μ and not T_γ lymphocytes are susceptible to the steroid effect (95). The decrease in lymphocyte numbers in man is due to redistribution of the circulating lymphocytes rather than to a lysis of lymphocytes, as occurs in the rat and mouse (96). Radiolabeled cell studies in the rat indicate that the fall in eosinophil numbers is due to reversible sequestration of the cells rather than to death (97). The numbers of lymphocytes, monocytes, and basophils in the circulation display a diurnal variation that is inversely related to diurnal levels of cortisol (98–100).

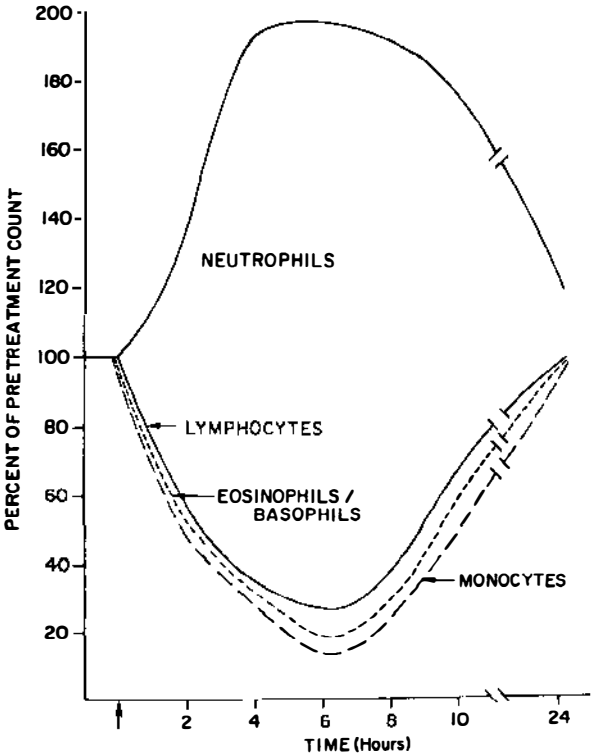

Figure 6 Typical changes in circulating leukocyte numbers following administration of steroid [taken from (88, 90–92)].

VASCULAR EFFECTS OF STEROIDS The vascular endothelium plays a gatekeeper role in the inflammatory response, since it controls the entry of plasma proteins as well as circulating leukocytes into a localized tissue site. Increased permeability of vascular endothelium can occur directly as a result of stimulation with histamine or with the combination of bradykinin and PgE_2 or PgI_2 (101, 102). However, the increase in permeability caused by LTB_4, the complement fragment C_{5a}, and the bacterial peptide FMLP requires PMN (and probably Pg derived from either the PMN, the vascular endothelium, or both) (64, 101–104). In vivo microscopic studies in animals clearly show that steroids reduce the sticking of leukocytes to vascular endothelium following the administration of an inflammatory stimulus (105–109). Thus, some of the effects of steroids in reducing edema may be related to an inhibition of the interaction between PMN and vascular endothelium required to increase vascular permeability.

In addition to the inhibition of inflammatory-cell adherence to endothelium, steroids are effective vasoconstrictors (110–113). This action is the basis of a

widely used test of topical steroid action (called the McKenzie test) (113) and may in part be related to the so-called permissive effects of steroids on adrenergic activity (111) (see below).

MAST CELLS, BASOPHILS, ANAPHYLAXIS The union of allergen and IgE on the surface of mast cells and basophils produces degranulation and the release of chemical mediators of inflammation [for review, see (114)]. The most dramatic result of this reaction in vivo is anaphylaxis; chronic elicitation of this response is an important component of most, if not all, allergic diseases. It is for this reason that much research into steroid mechanisms of action has been focused on the mast cell and basophil. A considerable amount of this work has been carried out in vitro and will be discussed in another section.

Skin mast cells Studies on the effect of steroid treatment on the number of mast cells in the skin of rats and human subjects have shown either no effect (115–118), a decrease (119–121), or, in some cases, a mild cytotoxic effect (122–123). Recent studies have shown that topical application of a potent steroid to human volunteers produces a reduction of tissue mast cells only after the production of cutaneous atrophy (124).

Basophils One of the cell types that infiltrates a skin-test site during experimental allergen challenge is the basophil. Significant numbers of basophils have been observed in skin windows, skin blisters, and skin biopsies following allergic challenge (125–128). Of particular interest is the observation of Dvorak and coworkers, who note a profound basophil infiltrate at the site of allergic-contact dermatitis involving delayed-type hypersensitivity reactions (129, 130). This basophil influx may be caused by a lymphocyte-derived basophil chemotactic factor (131). As I discussed above, steroid treatment inhibits the local influx of basophils to a tissue site (132, 133).

Anaphylaxis Naturally, it has not been possible to study the effect of steroids on experimental anaphylaxis in man, although the clinical evidence clearly suggests that they are not effective. There is some indication that treatment with steroid reduces the incidence and severity of radiocontrast dye reactions, a response that may be due to mediator release from basophils/mast cells. (134). Steroid treatment clearly protects against lethal anaphylaxis in the mouse and rabbit (135, 136), but not the guinea pig (137).

PMN Steroids clearly reduce the adherence of PMN to vessel walls and their subsequent efflux into LPR tissue sites in animals and man (see above). Some interesting, but as yet unresolved, questions are: what are the biochemical changes responsible for adherence and which cell type expresses them, the

leukocyte or the endothelial cell? Which cell type is the target cell for this most important action of steroids, the leukocyte or the endothelium? Recent studies indicate that the attachment of human PMN to bovine endothelial-cell monolayers is increased by prior exposure of the endothelial cells, but not the PMN, to LTB_4 (138), suggesting that the endothelial cell is the cell in which the adherence event is modulated. Several studies indicate that steroid treatment in vivo and in vitro can impair the adherence of PMN to nylon fibers (139–141). Therapeutically achievable concentrations of steroids in vivo and in vitro do not limit the chemotactic activity of PMN in vitro (141; R. P. Schleimer, D. W. MacGlashan, Jr., M. R. Mogowski, R. Daiuta, unpublished observations), nor do they inhibit the phagocytic activity of PMN (142). Low concentrations of dexamethasone have been reported to inhibit the release of plasminogen activator by PMN (143).

EOSINOPHILS The eosinophil has long been an enigmatic cell; however, recent studies strongly implicate the eosinophil as an active killer of parasites and a central causative cell type in allergic diseases. Eosinophils arrive, sometimes in great numbers, at tissue sites following mast-cell degranulation and the appearance of eosinophil chemotactic factors (144, 145). Several lines of evidence implicate the eosinophil in asthma: (*a*) the circulating eosinophil count correlates well with the severity of asthma (146); (*b*) patients who die of asthma show a marked eosinophilic infiltrate in airway tissue, especially at sites of pronounced epithelial damage (47, 147); (*c*) the eosinophil's major basic protein (MBP) is a potent cytotoxin for bronchiolar epithelium (148); and (*d*) levels of MBP found in the sputa of asthmatics are sufficient to cause damage to epithelial cells (148).

Steroid therapy prevents the entry of eosinophils into a site of inflammation (149)(see above). This may be related in part to the pronounced reduction in circulating eosinophil levels. Gleich and associates have shown that steroid therapy of asthmatics improves lung function [peak expiratory flow rate (PEFR)], at the same time reducing blood eosinophil numbers and serum and sputum levels of MBP (150).

MONONUCLEAR PHAGOCYTES The role of monocytes and macrophage in allergic diseases is not well characterized. Since antigen presentation is probably required for IgE production as well as for IgG production, macrophages (or perhaps dendritic cells) presumably are involved in the inductive phase of the allergic response. Recent studies demonstrating receptors for IgE on monocytes and macrophages, coupled with the appearance of these cells in the LPR and the recognition that under some circumstances they can release leukotrienes, leaves open the possibility of a significant role for these cells in allergic reactions (151, 152). The number of Fc_ϵ receptor–positive cells is elevated in

patients with severe allergic disease and is reduced to normal levels or lower by steroid therapy (151).

Steroid treatment reduces the numbers of circulating monocytes and tissue macrophages. The reduction of tissue-macrophage numbers is largely the result of a decrease in the precursor (monocyte) number (153, 154), which in turn is the result of reduced production in the bone marrow (155). As is the case with PMN, steroids do not inhibit monocyte phagocytosis, but they do interfere with intracellular killing of microorganisms (156).

Immunoglobulins The effects of steroids on specific IgE synthesis remain to be determined. Available information indicates that 2–4 weeks of steroid therapy have little or no effect on total IgE levels (157–159). While IgG antibody levels may be reduced slightly by similar steroid therapy (158–160), no evidence has been obtained for an inhibition of the specific IgG antibody response (161–163).

THE EFFECTS OF STEROIDS ON IN VITRO MODELS OF ALLERGIC DISEASE

Introduction

There is considerable uncertainty as to which cell types and chemical mediators are the most influential in causing allergic disease. By necessity, therefore, in vitro model systems employing a given cell type are only useful insofar as that cell is an important effector in the disease process. This section emphasizes the cells that have been strongly implicated in this role [i.e. mast cells, basophils, and mononuclear phagocytes (very little data are available on PMN and eosinophils)]. Although lymphocytes certainly play a part in the inductive phases of allergic processes and a wealth of knowledge on steroid effects on lymphocytes is available, less attention is given to these cells here, since their effector role is likely to be relatively small.

Steroid action in general requires the binding of steroids to an intracytoplasmic receptor, alteration of the ligand-receptor complex, translocation to the nucleus, and induction of RNA and then protein synthesis to produce an effector protein [for review, see (164, 165)]. Because of this, steroid effects in most in vitro systems require incubations of several hours to occur. Unfortunately, many studies were performed before this fact was known; these studies, in which steroid effects were usually demonstrated only at very high concentrations of drug, have been omitted from the present discussion.

Mast Cells and Basophils

Exposure of human basophils to steroids in culture for 24 hours leads to an inhibition of the subsequent histamine release induced by an IgE-dependent

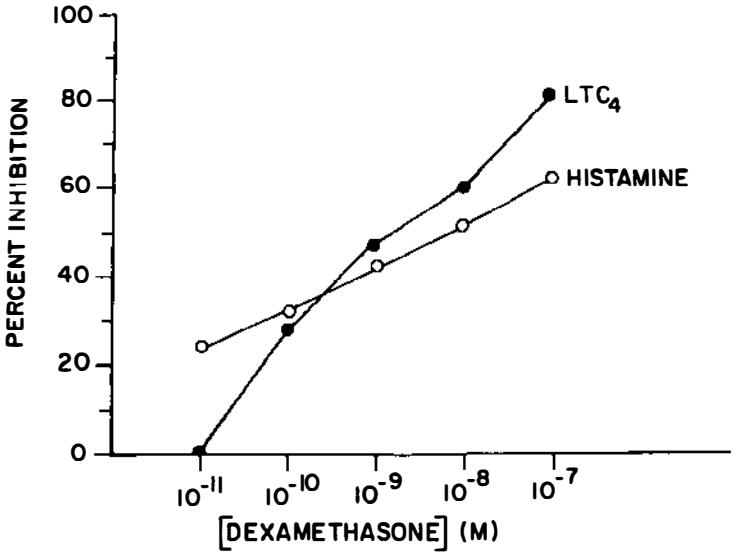

Figure 7 Inhibition of the release of histamine (○—○) and leukotriene C_4 (●—●) from anti-IgE–stimulated human basophils by dexamethasone.

stimulus but not of the release induced by a calcium ionophore, the chemotactic peptide Fmet-leu-phe, or phorbol diesters (166–68). This steroid effect is not caused by a modulation of the number of cell-surface IgE or IgE Fc receptors (167). Recent studies have shown that low concentrations of steroid inhibit the anti-IgE–induced release of leukotriene C_4 from basophils (169) (Figure 7).

Administration of steroid in vivo does not lead to an inhibition of basophil histamine release tested subsequently in vitro (92; K. L. Lampl, L. M. Lichtenstein, R. P. Schleimer, unpublished observations). Furthermore, basophils taken from asthmatics on continuous steroid therapy respond normally to anti-IgE (170). Lampl and coworkers have shown, however, that basophils derived from steroid-treated subjects are resistant to the in vitro action of dexamethasone, suggesting that steroid treatment in vivo has altered their in vitro responsiveness and perhaps their functions other than histamine release as well (171).

Although the IgE-dependent release of histamine and arachidonic acid in vitro is inhibited by steroids in murine mast cells (172, 173), this is not the case in human pulmonary mast cells (174). Incubation with dexamethasone does not inhibit the release of histamine, PgD_2, or leukotriene C_4 from human lung mast cells, whether they are in situ in lung fragments or in a highly purified state (174). This finding is consistent with the lack of effect of steroids in vivo against the immediate response to antigen (see above). In contrast, in the mouse and rat the protective effects of steroids in anaphylactic models may be related to an inhibition of the immediate mast-cell degranulation response.

Lung Tissue

Challenge of perfused lung tissue or lung fragments in vitro with antigen or anti-IgE leads to the release of mediators derived from mast cells (histamine, leukotriene C_4, prostaglandin D_2, and others) and other sources (6-keto-prostaglandin $F_{1\alpha}$, prostaglandin E_2, and $F_{2\alpha}$) (174–178). Overnight incubation of human lung fragments with relevant concentrations of steroids does not inhibit the subsequent release of the mast cell-derived mediators histamine, SRS (leukotriene C_4), PgD_2, or TxB_2, but it does produce a pronounced inhibition of the release of other arachidonate metabolites, including 6-keto-prostaglandin $F_{1\alpha}$ (174, 179). As is discussed below, inhibition of the release of arachidonic acid metabolites is likely to be an important mechanism of antiinflammatory steroid action.

Mononuclear Phagocytes

The in vivo studies discussed above indicate that steroids inhibit the entry of monocytes into tissue and their subsequent differentiation to become macrophages. In vitro studies support this concept, showing that steroids inhibit monocyte chemotaxis and differentiation (180–182). Other in vitro studies indicate that steroids inhibit the mononuclear-cell antigen-presenting function for T lymphocyte proliferation (183). Monocyte HLA DR surface antigen is increased by steroid treatment, and antigen presentation is normal if steroid-treated monocytes are washed free of steroid before being pulsed with antigen (183).

Because of the difficulty in obtaining human macrophages, most of the studies discussed below have been carried out using murine peritoneal macrophages. The mechanism by which steroids interfere with antigen presentation is not clear. Several studies indicate that macrophage phagocytic activity and phagosome-lysosome fusion is unaffected by steroids (184–86). Perhaps an important mechanism by which steroids inhibit macrophage activity in presenting antigen and inducing T-cell proliferation is the inhibition of Ia antigen induction and the synthesis of interleukin-1 (187, 188).

Steroids inhibit the in vitro release of some macrophage-derived mediators but not of others. Steroids inhibit the mediators released at cell activation and not the constitutively produced mediators (or the constitutive functions, such as phagocytosis) (Table 1). In addition to inhibiting macrophage plasminogen–activator release, steroids have been reported to induce a plasminogen-activator inhibitor in hepatoma cells, possibly potentiating the antifibrinolytic actions of steroids (192). Finally, human pulmonary macrophages produce a mucus secretagogue (193). It is possible that some of the action of steroids in inhibiting mucus release in vivo and in vitro is in inhibiting the release of this secretagogue from macrophages (193, 194).

Table 1 Effects of steroids in vitro on the release of macrophage-derived mediators

Mediator	Release		Inhibited by steroids	Reference
	Activation-dependent	Constitutive		
Interleukin-1	+		+	187, 188
Plasminogen activator	+		+	189, 190
Elastase	+		+	190
Collagenase	+		+	190
Lysozyme		+	–	190
Colony-stimulating factor	+		+	191
Fibronectin		+	–	191a
Macrophage-derived growth factor		+	–	191a

Lymphocytes

The suppressive effects of steroids against lymphocyte-mediated reactions (e.g. delayed hypersensitivity, graft rejection) are probably in large part due to an inhibition of lymphocyte proliferation (195). Proliferation is inhibited by the combined effects of a reduction in both antigen presentation and the synthesis of interleukin 1 and interleukin 2 (195–198) (see above). Steroids inhibit the generation of cytotoxic lymphocytes but not their action (199–201). T lymphocytes in mouse and rat are lysed by the steroid-induced activation of an endogenous endonuclease that destroys the DNA; human T lymphocytes are resistant to the lytic actions of steroids (202, 203).

MOLECULAR THEORIES OF STEROID ACTION

Introduction

In the late sixties and early seventies, a unified concept for all steroid action emerged (164, 165). Thus far, all cells that show a response to steroids (whether they be sex steroids, mineralocorticoids, or glucocorticoids) contain a specific intracytoplasmic steroid receptor. The unified concept states that steroid action is mediated through receptor binding and eventual alteration in the synthesis of proteins. Recent work indicates that steroids also can alter posttranslational processing of protein synthesis (e.g. glycosylation, cleavage, and compartmentalization). This presumably also occurs via steroid-receptor action at the level of gene expression (204, 204a).

For many years before the emergence of this unified concept, antiinflammatory steroid action was thought to be the result of lysosomal stabilization, since high concentrations of steroids acutely prevent the emptying of isolated lyso-

somes caused by irradiation and other agents (205). Lysosomal stabilization is no longer a tenable hypothesis, however, because it occurs in the absence of a nucleus and functioning protein-synthetic apparatus, high concentration of steroids are required, the time course of action (immediate) is not consistent with the in vivo time course, and for other reasons (206).

Phospholipase Inhibition

Appreciation of the critical importance of arachidonic-acid metabolites in inflammation is increasing. Just a little over a decade ago, Vane and Smith & Willis demonstrated that a major mechanism of action of non-steroidal antiinflammatory drugs such as aspirin is an inhibition of the synthesis of prostaglandins (207, 208). At about the same time, Kunze & Vogt pointed out that the rate-limiting step in the production of arachidonic acid metabolites (cyclooxygenase metabolites as well as lipoxygenase metabolites such as leukotrienes and HETES) is the phospholipase A_2 enzyme that liberates arachidonic acid from phospholipid stores (209).

Gryglewski and coworkers, Lewis & Piper, and Levine and associates demonstrated that prolonged exposure to steroids leads to inhibition of prostaglandin release in several different tissues (210–212). It rapidly became clear that this steroid action was due to inhibition of the release of arachidonic acid rather than to inhibition of the cyclooxygenase enzyme (213, 214). Inhibitors of protein or RNA synthesis block the steroid effect, suggesting that steroids induce the synthesis of an inhibitor of arachidonic-acid release (215, 216). Subsequent studies by Flower & Blackwell, Hirata and coworkers, and others have uncovered several steroid-induced proteins that inhibit the liberation of arachidonic acid in many different tissues (217–223). One of these proteins, termed macrocortin, was first identified in the perfusate of steroid-treated guinea pig lungs and subsequently in rat leukocytes (217, 219). This polypeptide (MW 16,000, from guinea-pig lung) is stored by rat peritoneal leukocytes and rapidly released following exposure to steroids (219). Macrocortin has been shown to act directly in inhibiting the release of radiolabeled fatty acid from phosphatidylcholine.

Characterization of phospholipase inhibitory proteins from rabbit PMN and rat leukocytes reveals a protein of 40k MW (termed lipomodulin), as well as proteins of 200k, 30k, and 16k (218, 224, 225). Collaborative studies suggest that macrocortin (16k) as well as the 30k-protein are split products of lipomodulin (224). The phospholipase inhibitors are inactivated by phosphorylation and are often phosphorylated during their generation; they can be activated in vitro with alkaline phosphatase and apparently in vivo by target cells (221, 224, 226, 227). Lipomodulin is active in vivo in preventing carrageenan pleurisy in rats (227).

The applicability to humans of this data on phospholipase-inhibitory proteins

is not yet entirely clear. Steroids have been shown to inhibit arachidonic acid–metabolite release by both pathways in several human cell and tissue types (169, 212, 228, 229). Furthermore, Hirata et al have demonstrated the presence of antilipomodulin antibodies in patients with rheumatic disease (230). Their finding in mice that antilipomodulin binds to I-J determinants and causes selective loss of suppressor cells raises the intriguing possibility that this may also be occurring in the patients with circulating antilipomodulin (230, 231).

Another function of phospholipase-inhibiting proteins may be in the regulation of IgE biosynthesis. Rat and allergic human lymphocytes produce IgE binding factors (232–236). In the nonglycosylated state, the rat IgE binding factor inhibits the formation of IgE-producing cells (232, 234, 237). Steroids, or a 16k fragment of lipomodulin, prevent glycosylation of the IgE binding factor, thus yielding the suppressive form of the factor. Antilipomodulin has the opposite effect (226, 233). The regulation of glycosylation by glucocorticoids is not without precedent (204). Thus far, the effects of steroid therapy on specific IgE synthesis in man have not been determined. However, owing to the apparent lack of effect on IgG synthesis and the rapid therapeutic action of steroids in allergic diseases (hours to days), it seems unlikely that regulation of IgE synthesis in vivo is a critical mechanism of steroid antiallergic actions.

The β-Adrenergic Theory of Asthma

An interaction between steroids and the β-adrenergic arm of the autonomic nervous system may explain some of the steroids' antiasthmatic effects. Researchers have known for some time that asthmatic patients show a reduced response to the effects of β-agonists, whether or not they have been receiving adrenergic drugs (228, 239). Steroid therapy restores the effects of β-agonists in asthmatics (240–242) (Figure 8). Based on these and other observations, Szentivanyi proposed that asthma is due to reduced β-adrenergic tone and that the efficacy of steroids is due to their permissive, or restorative, effects on the β-adrenergic system (243, 244).

A reduced response (desensitization) can be induced in vivo or in vitro by continued exposure to β-agonists. When normal subjects are desensitized in such a fashion, a single dose of intravenously administered steroid restores their response to inhaled β-agonists (245, 246).

Although the most important antiasthmatic action of β-agonists may be their dilating effects on smooth muscle, β-agonists also inhibit the function of inflammatory cells such as mast cells, basophils, PMN, and lymphocytes by elevating intracellular cyclic AMP levels [for review, see (247)]. Lymphocytes and PMN from asthmatics show a lower cyclic AMP response to β-agonists than do normals; the response is restored by previous in vivo steroid therapy (248–250). Steroids increase the number of β receptors on lung tissue in vitro

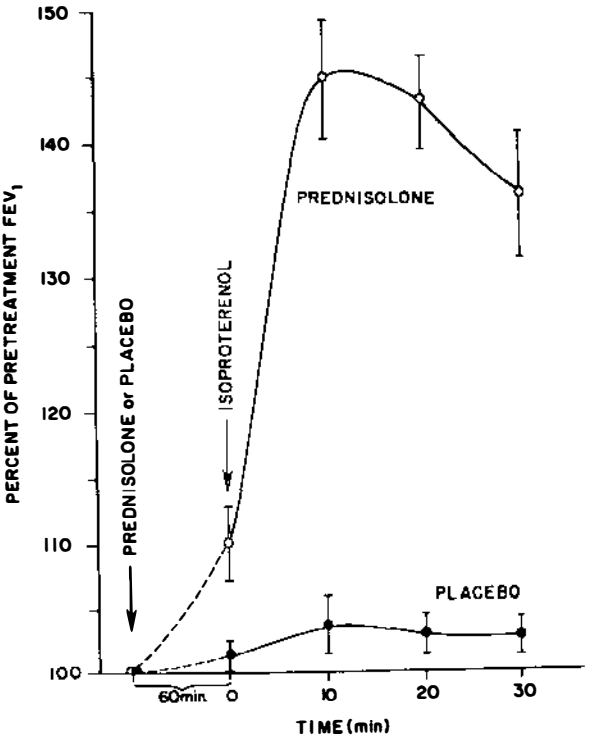

Figure 8 Permissive effect of steroid therapy on the β-adrenergic response in asthmatics. Isoproterenol response is weak in untreated patients (placebo), while one-hour pretreatment with 40 mg prednisolone allowed a brisk bronchodilatory response to isoproterenol [taken from (245)].

and cause some β_1 receptors to become β_2 receptors in 3T3 cells (251–253). However, in PMN, steroid prevents the desensitization-induced uncoupling of receptors from adenylate cyclase rather than altering receptor numbers (254). Thus, the so-called permissive effects of steroids on the β-adrenergic response in asthmatics may be related to steroid modulation of β receptor number, receptor subtype, or β-receptor coupling to the adenylate cyclase.

SUMMARY AND CONCLUSIONS

The beneficial actions of steroids for patients with allergic diseases cannot be explained by any single mechanism. A graphic summary of the most important antiallergic actions of steroids is shown in Figure 9. In this case, steroid action against asthma is discussed—the mechanisms may be the same or very similar in allergic disease of the skin and nasal airways. The immediate reaction, involving mast cell–mediator release, constriction of airways smooth muscle,

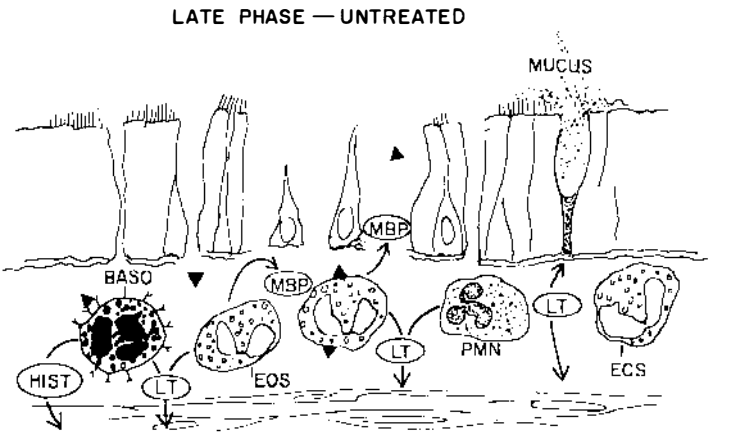

Figure 9 Model of steroid action on the late-phase response to bronchial-inhalation challenge with allergen (see Figure 2 for acute-response model). In the absence of steroid treatment (top), an inflammatory-cell infiltrate occurs, leading to bronchoconstriction, mucus secretion, edema, and epithelial destruction. Steroid therapy (bottom) prevents the inflammatory cell infiltrate and the concomitant sequelae.

increase of epithelial permeability, and mucus secretion (see Figure 2), is relatively unaffected by steroids. In the untreated subject, this immediate reaction is followed by the late-phase reaction (top panel, Figure 9). In this reaction, an inflammatory-cell infiltrate occurs (neutrophils, eosinophils, basophils, and monocytes are attracted by chemotactic factors). Eosinophil-derived MBP produces widespread focal destruction of airway epithelium, cell-derived mediators maintain mucus hypersecretion and epithelial hyper-meability, and bronchial hyperractivity and reduced β-adrenergic tone are manifest by mechanisms not yet understood.

In the steroid-treated subject, the inflammatory-cell infiltrate is profoundly reduced, and the usual consequences of that infiltrate, i.e. epithelial cell destruction and increased permeability, mucus hypersecretion, bronchoconstriction, and edema, therefore do not occur (Figure 9, bottom). In addition to this, the function of those cells that do enter the tissue (e.g. basophils, monocytes) is reduced. Furthermore, many of the target tissue responses themselves (e.g. mucus secretions and epithelial-cell permeability) appear to be inhibited directly by steroids. Finally, the smooth-muscle and perhaps the inflammatory-cell response to adrenergic tone (both neural and circulating catecholamines) is potentiated by the steroids.

It is somewhat difficult to factor out the relative importance of the inhibition of arachidonic acid–metabolite release in this picture. Since the vascular-permeability response leading to edema often requires a chemotactic stimulus and cyclooxygenase metabolites, or neutrophils, steroid effects on vascular permeability may be mediated in part via inhibition of arachidonic acid–metabolite formation. The lack of effect of aspirin in patients with asthma limits the potential importance of this mechanism to lipoxygenase products. However, the inhibition of phospholipase has as a consequence more than just the inhibition of arachidonic acid–metabolite release; many cells are activated by phospholipase-dependent mechanisms. Such may be the case with vascular endothelial cells, mucus-producing goblet cells, epithelial cells, and others. If that is the case, then steroids may exert many of their actions (e.g. inhibition of inflammatory cell adherence to vascular endothelium, inhibition of mucus secretion, etc) by way of a phospholipase-inhibiting intermediate.

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