

Effect of intranasal corticosteroids on release of cytokines and inflammatory mediators

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Abbreviations: AP-1, activation protein 1; ECP, eosinophilic cationic protein; EDN, eosinophil-derived neurotoxin; GCS, glucocorticosteroids; GM-CSF, granulocyte/macrophage colony-stimulating-factor; GR, glucocorticosteroid receptor; GRE, glucocorticosteroid responsive element; HRF, histamine releasing factor; ICAM, intercellular adhesion molecule; I- κ B, inhibitor of NF- κ B; IL, interleukin; LTC₄, leukotriene C₄; MBP, major basic protein; NF- κ B, nuclear factor kappa B; PAF, platelet activation factor; RANTES, regulated on activation normal T cell expressed and secreted; TNF- α tumor necrosis factor alpha; VCAM, vascular cell adhesion molecule.

Introduction

Glucocorticosteroids (GCS) have been used successfully for nearly 50 years in the treatment of airway diseases, and still their role in treatment is actively discussed; their routine clinical use varies in different countries. Clinical introduction was successful; however, it was followed by subsequent misuse with high doses and elucidation of severe adverse effects, based mainly on the lack of knowledge on GCS actions. In subsequent decades, researchers have elucidated parts of the complicated pharmacological and biochemical mechanisms of GCS and have clarified the possibilities and limitations in differentiating desired from undesired steroid actions. Based on a combination of empiricism and directed pharmacological research, there has been fruitful development of topical therapy for asthma and rhinitis, limiting by far the undesired effects to the advantage of clinical benefit. Today, topical GCS for the treatment of rhinitis and nasal polyposis are considered safe and effective, and anti-inflammatory efficacy is superior to other anti-allergic treatments. However, our knowledge about the mechanisms of action of GCS is still insufficient.

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Allergic rhinitis and nasal polyposis

Allergic rhinitis: an inflammatory process

Allergic rhinitis results from an IgE-mediated degranulation of mast cells associated with nasal inflammation of variable intensity (1). This is characterized by the presence of basophilic cells and eosinophils in nasal smears, an epithelial accumulation of mast cells and eosinophils, tissue eosinophilia, an increase in mucosal Langerhans's cells, T-lymphocyte accumulation and activation, and upregulation of the vascular endothelial expression of leukocyte adhesion molecules (2–8).

In past decades, the mechanisms of allergic rhinitis have been partially clarified. Studies by Naclerio et al. (9), using nasal allergen challenge followed by measurement of cells and mediators in the nasal fluid, have made it easier to analyze the events occurring during the allergic reaction. However, such a challenge differs from the natural course of the disease in that it is a single provocation and does not reflect the multiple triggers which occur during the pollen season (1). In the early days, mediators such as histamine, prostaglandins and leukotrienes were demonstrated to be released into nasal secretions after allergen challenge, and their biological effects have been elucidated over the years. In the nose, histamine is one of the most important mediators for the so-called early phase reaction, but may also be released hours after allergen challenge due to histamine releasing factors (HRF) that were later partially characterized as chemokines (47, 48). Today, the measurement of tryptase can be used to monitor instant mast cell activation in the early phase, and ECP (eosinophilic cationic protein) is a reliable marker for the so-called late-phase reaction, characterized by the recruitment and activation of cells into the mucosa (7, 12, 13). Wang et al. (13) focused on the measurement of histamine, tryptase, LTC₄ and ECP under natural conditions and found correlations with symptoms as well as with the number of inflammatory cells. Although these mediators could be used to explain nasal symptoms after challenge, and eosinophilic mediators in particular were suitable to monitor eosinophil activation in natural settings, these mediators could not serve as explanation for the cellular immune reaction in nasal late phase and season.

In recent years, researchers have increasingly been able to identify cytokines, chemokines and adhesion molecules as elements to orchestrate the cellular inflammation. Pro-inflammatory cytokines such as IL-1, IL-6 and TNF- α (14, 15) are released within hours after allergen challenge and serve as unspecific alarm signals, as they are also released in

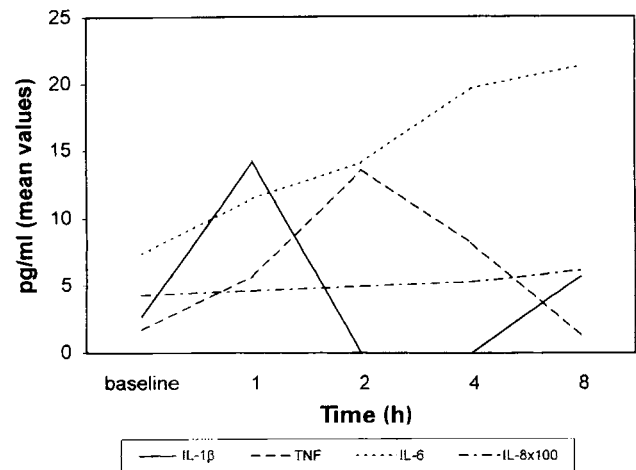


Figure 1. Proinflammatory cytokines in nasal secretions of allergic rhinitis patients after challenge (8).

viral and bacterial rhinitis (Fig. 1). Their actions are multi-functional and include the activation of endothelial cells, the release of a cytokine cascade and the activation of T-cells that are present in the nasal mucosa. Hours after challenge, further cytokines such as IL-4, IL-5, GM-CSF and IL-3 can inconstantly be measured in secretions, but the upregulation of mRNA for these cytokines has been demonstrated convincingly by Durham et al. (16). At this stage, nasal inflammation begins to develop into an allergic reaction, which is different from viral and bacterial inflammation. The release of pro-inflammatory and regulatory cytokines induces, within minutes to hours, the start of the so-called adhesion cascade, which is a complex process of loose binding, firm adhesion and transmigration of cells (17). The best-characterized adhesion molecule families involved in allergic reactions are the integrins, the immunoglobulin supergene family and the selectins. Adhesion molecules have been shown to be upregulated in seasonal and perennial allergic rhinitis, not only on endothelial cells but also on the epithelium, with ICAM-1 serving as a marker of inflammation (8, 18–20). Recent findings in season clearly characterize allergic rhinitis as an inflammatory disease: the release of eosinophilic mediators and the release of pro-inflammatory cytokines is significantly increased not only in season, but also postseasonally for at least 6 weeks. From these findings, allergic rhinitis may be defined as a persistent inflammatory reaction (21).

Nasal polyposis: IL-5 regulates eosinophilic inflammation

Nasal polyposis is characterized by chronic eosinophilic inflammation and is frequently associated with asthma

and aspirin sensitivity. Corticosteroid-dependent asthma, aspirin sensitivity and nasal polyposis form the so-called "Samter triad". In about 80% of bilateral nasal polyposis, a moderate to severe eosinophilic infiltration of the polyp stroma can be identified (22). This may be explained by an increase of eosinophilic migration into the tissue, by prolonged survival of these cells, or by a combination of both. Eosinophils release toxic products and superoxid radicals and may contribute not only to tissue damage but also to the growth of nasal polyps. In contrast to allergic rhinitis, nasal polyps represent a form of unlimited eosinophilic inflammation, the pathomechanism of which is only partially understood. In the past decade, researchers focused on the characterization of cytokines involved in the recruitment and prolonged survival of eosinophils.

Comparing protein levels of different cytokines and chemokines in nasal polyps versus control mucosal tissue, we were able to demonstrate an impressive upregulation of IL-5 synthesis in nasal polyps (Table 1) (22–24). Furthermore, polyp but not control nasal tissue expressed IL-5 mRNA. Simon et al. (25) used neutralizing concentrations of anti-IL-5 mAb and found decreased eosinophil numbers due to apoptosis in a polyp model. According to our findings, IL-5 plays a key role in prolonged eosinophil survival (26) and, most probably, together with chemokines such as eotaxine and RANTES in the recruitment of eosinophils (27, 28). Furthermore, we could demonstrate the upregulation of the transmembrane isoform of the IL-5 receptor α , which is crucial for the action of IL-5 on eosinophils. As eosinophils have been demonstrated to release IL-5 and, at the same time, upregulate the transmembrane IL-5 receptor α , an autocrine pathomechanism could be the driving force for chronic eosinophilic inflammation in nasal polyps (Fig. 2) (22, 23).

Table 1. Cytokine proteins in nasal polyps and in normal controls (24)

Cytokine	Nasal polyps	Normal controls	P value
IL-1 β	+	++	<0.05
IL-1Ra	++	+++	<0.05
TNF	+	+	NS
IL-4	–	–	NS
IL-5	++	–	<0.01
IL-6	+	+	NS
IL-8	+	+	NS
IL-10	+	++	NS
RANTES	++	++	NS

Molecular mechanisms of glucocorticosteroid action

The action of GCS is mediated through cytoplasmic receptors which are found in many different cells (Fig. 3) (29, 30). Steroids are lipophilic and cross the cell membrane rapidly to bind to the GCS receptor and dissociate a protein that has held the receptor in an inactive state. The GCS receptor complex then enters the cell nucleus and acts as a transcription factor, binding to specific recognition sequences on the DNA in the promotor region of GCS responsive elements (31, 32). GCS may either activate or suppress target genes by increasing or decreasing the specific messenger ribonucleic acid production (mRNA). This interaction decreases the transcription of many inflammatory mediators such as cytokines and increases the production of a number of anti-inflammatory mediators and other proteins such as lipocortin-1 and β -adrenoceptors (30). Recently GCS has been shown to upregulate the expression of I κ B, which inhibits nuclear factor kappa B (NF- κ B) transcriptional ability (32, 33). Furthermore, the GCS receptor complex can interact directly with transcription factors such as NF- κ B and activation protein AP-1, which are activated by cytokines upon binding to the cytokine receptor (29). By interacting with both NF- κ B and AP-1, thus preventing their action as transcription factors, GCS inactivate effects of cytokines on the cell and prevent further cytokine production.

Interestingly, apart from these time-consuming mechanisms, few actions of GCS are so rapidly induced that direct and nonreceptor-mediated effects have been proposed; for example, the reduction of vascular exsudation in rodents can

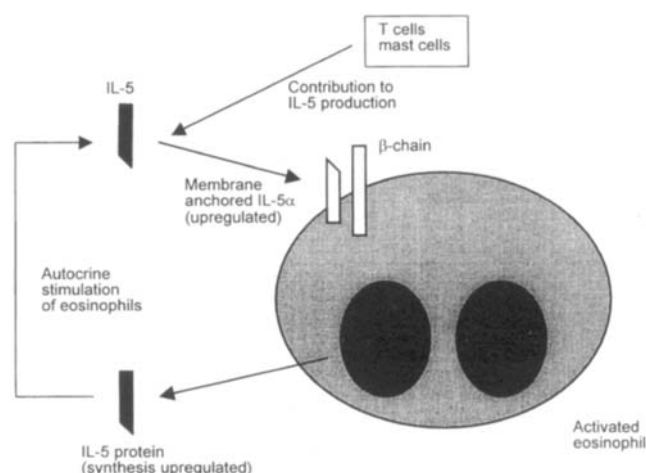


Figure 2. Eosinophils may be able to create an autocrine loop for their activation and survival within nasal polyp tissue (22).

be inhibited by GCS after incubation times of only 5–10 min. GCS modulation can result in up- or downregulation of a gene, depending on the type and on the developmental status of a cell. Different cell types and cytokines are regulated differently by GCS, and this may be either a direct or an indirect effect, for example by down-regulating the cell number in a given tissue. It is a misbelief that GCS inhibit everything in every cell.

Effects of intranasal glucocorticosteroids

Intranasal GCS interfere with multiple steps in the inflammatory process. They decrease capillary permeability, decrease the glandular response to cholinergic stimulation, interfere with arachidonic acid metabolism which results in decreased mediator production, reduce mediator release, decrease production of cytokines from TH-2 lymphocytes

and inhibit the influx of eosinophils and basophilic cells to the nasal epithelium [34].

Effects of intranasal glucocorticosteroids on cells and mediator

GCS can either act directly on cell activation and mediator production, or indirectly inhibit inflammatory cell accumulation especially in those cases, where the cell numbers exceed those seen under normal conditions. Topical GCS have been shown to suppress the increase in eosinophils, macrophages, Langerhans cells and lymphocytes in allergic rhinitis [35]. Furthermore, the number of recruited mast cells and basophils is reduced due to sufficient treatment. Comparing the effects of intranasal GCS on the lamina propria and the epithelium, several studies [36, 37] have suggested that intranasal GCS might be more active on the superficial compartment of the nasal mucosa than on deeper compartments. Rak et al. [36] found that topical GCS

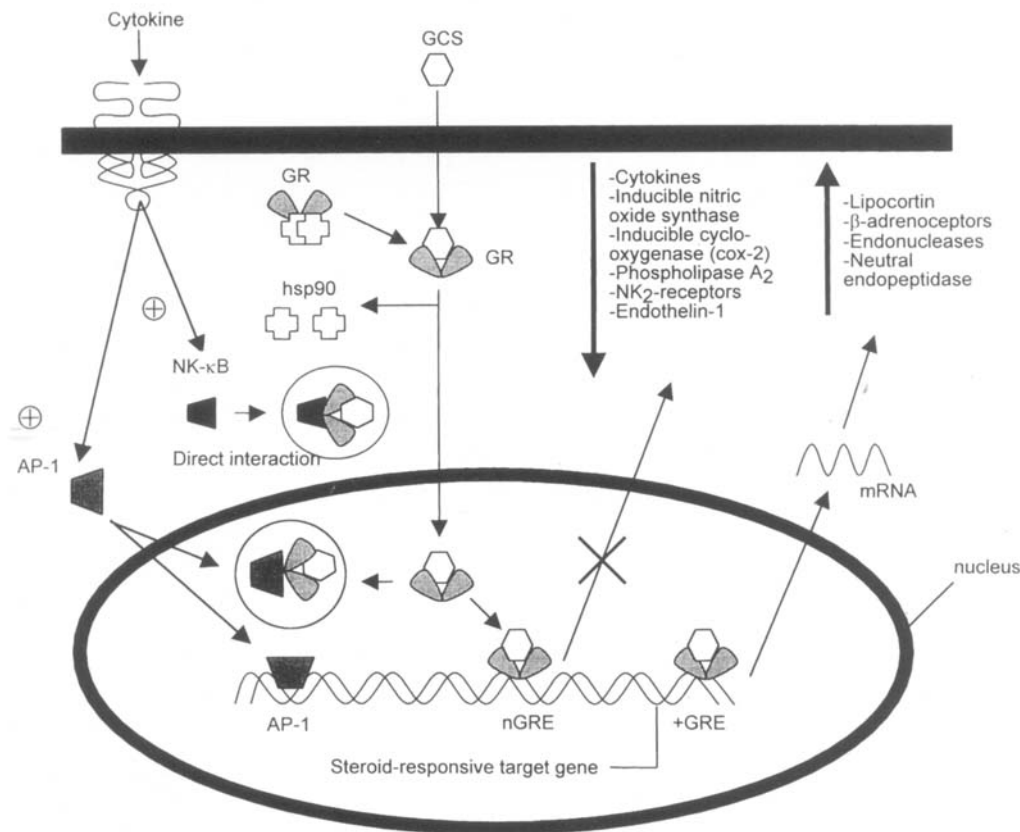


Figure 3. The molecular mechanism of action of glucocorticosteroid (GCS) [modified from 30]. GCS are lipophilic and cross the cell membrane to bind to the glucocorticosteroid receptor (GR) and dissociate the heat shock protein (hsp 90) that has held the receptor in an inactive state. The glucocorticosteroid–receptor complex then enters the cell nucleus and acts as a transcription factor, binding to specific recognition sequences on the DNA in the promoter region of GCS responsive elements (GRE). Glucocorticosteroids may either activate (+ GRE = positive glucocorticoid responsive element) or suppress (nGRE = negative glucocorticoid responsive element) target genes by increasing or decreasing the specific messenger ribonucleic acid production (mRNA). Recently GCS has been shown to upregulate the expression of IκB, which inhibits nuclear factor kappa B (NF-κB) transcriptional ability. Furthermore, the GCS receptor complex can interact directly with transcription factors such as NF-κB and activation protein AP-1, which are activated by cytokines upon binding to the cytokine receptor.

therapy was associated with markedly fewer mucosal inflammatory cells, such as CD3⁺ (total T cells), CD4⁺ (T-helper cells), CD8⁺ (T-suppressor cells) and CD25⁺ (activated T cells). As T-cell kinetics, activation and cytokine production are highly sensitive to GCS, it seems likely that an important part of the clinical benefit is due to a suppressive effect on T-cell function (38). Whereas T cells and macrophages can be directly affected by GCS in terms of proliferation and protein synthesis, but also in terms of activation and recruitment, eosinophils and mast cells may be affected only indirectly by GCS inhibition of their recruitment. This makes it understandable that GCS do not act immediately on the release of mediators such as histamine, but may still effectively suppress sneezing and itching after consequent GCS treatment over several days. Klementsson et al. (12) demonstrated that topical GCS treatment reduces the proportion of eosinophils, ECP levels and the secretory response to methacholine compared to placebo. The suppression of eosinophil recruitment in nasal late phase and under natural conditions is a hallmark of GCS action, clearly indicating its profound anti-inflammatory activity. Topical steroids reduce the number of eosinophils and, to a greater degree, the number of activated eosinophils (36). These results confirm that topical GCS inhibit allergen-induced early and late nasal responses. A large body of studies has also demonstrated the decrease of mediator release due to GCS action. This includes histamine, tryptase, PAF, arachidonic acid metabolites and eosinophil products such as major basic protein (MBP) and eosinophil derived neurotoxin (EDN) (34). Again, these actions are more indirect than direct by reducing the recruitment of the mediator sources.

Correlated to the inhibition of cell recruitment and activation, nasal hyperresponsiveness to specific and unspecific stimuli is also reduced. The pathomechanism behind this reduction, however, has not been elucidated fully.

Effects of intranasal glucocorticosteroids on cytokines and adhesion molecules

The suppression of transcription of cytokine mRNA to protein is a prominent action of GCS (Table 2) (39). This affects not only pro-inflammatory cytokines such as IL-1 β , IL-6 and TNF- α , but also atopy-related cytokines such as IL-3, IL-4, IL-5 and GM-CSF (16). Furthermore, the production of chemokines such as IL-8 or RANTES is inhibited significantly (27, 40, 41). Because of these effects, recruitment and localization of inflammatory cells into reactive tissue is inhibited, as well as their activation and protein

synthesis. Especially for eosinophils, this also has a prominent effect on the survival of these cells, as has been shown in nasal polyposis. Several studies (34, 36, 42) have demonstrated that the levels of nasal eosinophils, eosinophil products and eosinophil survival-enhancing cytokines (IL-5, IL-3 and GM-CSF) were significantly lower after treatment of allergic rhinitis with topical GCS such as fluticasone propionate, budesonide and beclomethasone dipropionate.

The inhibition of production and release of pro-inflammatory and regulatory cytokines has an important impact on the expression of adhesion molecules such as E-selectin, VCAM-1 and ICAM-1 (18, 43). We have recently established an *ex vivo* model using freshly obtained nasal mucosa, which is stimulated with allergen extracts and investigated in terms of E-selectin expression. Allergen exposure increased the expression of E-selectin on endothelial cells within 1 h from about 10% to 80% of total endothelial cells (Fig. 4). Interestingly, GCS were able to suppress this expression totally in a dose-dependent manner with a preincubation time of only 30 min. When stimulation was performed with IL-1 or TNF- α , the suppression of E-selectin by GCS was only about 20–30%. This indicates that GCS are most probably indirectly inhibiting adhesion molecule expression by blocking the release of proinflammatory cytokines with an extremely fast onset of action.

Clinical implications

Intranasal GCS affect the complex inflammatory reactions of allergic rhinitis and nasal polyposis at various levels, amounting to an overall reduction of inflammation and consequently reduction of symptoms. In particular, topical GCS do not only reduce the late phase reaction, but also the early phase symptoms of allergic rhinitis comparable to the efficacy of antihistamines (36, 41). Some studies could

Table 2. Cells, mediators and cytokines directly and indirectly affected by topical glucocorticosteroids

Cells
T-lymphocytes, eosinophils, macrophages, monocytes, basophils, fibroblasts, mast cells, Langerhans cells, neutrophils
Mediators
AA metabolites, PAF, histamine, tryptase, EDN, ECP, sICAM
Cytokines
IL-1, IL-6, TNF, IL-2, IL-10, IL-3, IL-4, IL-5, GM-CSF, IL-8, RANTES, IFN, FGF, TGF, SCF and others

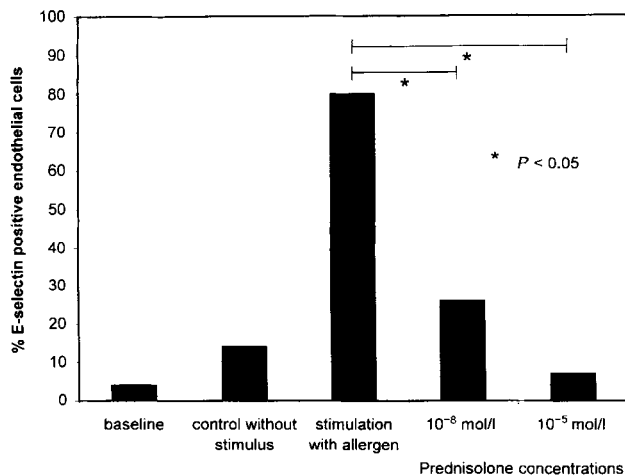


Figure 4. Action of prednisolone on allergen-induced E-selectin expression in mucosal tissue (n = 6). Incubation time with allergen = 2 h. Preincubation time with prednisolone = 30 min.

demonstrate that topical GCS such as fluticasone propionate and budesonide were more effective than H₁-blockers, especially for nasal obstruction [38, 44–46]. However, GCS must be used regularly because of their mode of action, and only then can the full effectiveness of GCS action be expected. In fact, topical GCS treatment is superior to other anti-allergic treatment modalities in terms of symptom reduction and inhibition of inflammation, measured as a reduction in the release of inflammatory mediators. This favorable profile of effects is combined with a good tolerability locally as well as systemically, if used at recommended dosages and applied using the correct technique.

In terms of onset of action, a clinically significant reduction of symptoms can be observed within 12 h, but further reduction can be observed during subsequent days. As discussed above, more rapid effects of GCS can also be demonstrated. However, the full effectiveness of topical GCS treatment may not be reached before weeks, in allergic rhinitis and months of treatment in nasal polyposis.

Allergic rhinitis

Many studies have shown that topical GCS are highly effective in seasonal allergic rhinitis, with therapeutic

results ranging from good to excellent in 70–90% of the patients [38]. In contrast, it is more difficult to treat perennial rhinitis. Tarlo et al. [47] found that 54% of patients with perennial rhinitis achieved acceptable symptomatic improvement from a GCS spray, but this percentage was increased by a short course of systemic GCS.

Nasal polyposis

Topical GCS treatment reduces nasal symptoms, polyp size and number of recurrences after polypectomy in most patients. In contrast, management of patients with severe nasal polyposis is still unsatisfactory, and needs to involve systemic GCS treatment and sinus surgery [38].

Conclusions

Intranasal glucocorticosteroids have a wide range of actions, either directly or indirectly, on recruitment and activation of cells, release of mediators and cytokines, on the expression of adhesion molecules and on the survival of inflammatory cells. There is no single antagonism sufficient to interfere with the complex pathomechanisms of inflammatory processes in allergic rhinitis and nasal polyposis, but rather a bundle of effects necessary to be highly effective in the treatment of these diseases. Suppression of the recruitment and activation of eosinophils is a hallmark of topical GCS treatment, but also mast cells, basophils and macrophages are inhibited, correlating with reduction in inflammation and symptoms. There is now convincing evidence that GCS have an inhibitory effect on the symptoms of early response, which becomes apparent after prolonged treatment. Topical GCS treatment today is the most effective anti-allergic and anti-inflammatory therapy available. Increasing understanding of the mechanisms of GCS action helps in selecting patients for treatment, establishing therapeutic dosages and treatment duration, and avoiding side effects.

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