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Mechanisms of Glucocorticoid Action in Chronic Rhinosinusitis

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The innate immune system and its complex interplay with the adaptive immune system are increasingly being recognized as important factors in the pathogenesis of chronic rhinosinusitis (CRS). Adaptive immune components, including resident and inflammatory cells, and their associated mediators, have been the subject of most research in CRS. For this reason, theories of CRS pathogenesis have involved the concept that inflammation, rather than infection, is the dominant etiologic factor in CRS. Therefore, glucocorticoids are increasingly used to treat CRS. This review will outline our current knowledge of action mode of glucocorticoids in CRS.

Key Words: Chronic rhinosinusitis; glucocorticoids; glucocorticoid receptor; cytokines

The cause and pathophysiology of chronic rhinosinusitis (CRS) are very heterogenous and have been intensively investigated. Although they remain debatable, abnormal host responses to various triggers, including inflammatory signaling of nasal mucosa, rather than the trigger itself, have been suggested to be ultimately responsible for the persistent inflammatory process of CRS.[1-4] Therefore, glucocorticoids are increasingly being used to treat CRS.[5] Clarification of mechanisms for glucocorticoid action might provide a new insight into the mode of glucocorticoid action and allow selection of rational methods to treat patients with CRS.

CRS is considered a group of heterogeneous disorders characterized by prolonged symptomatic inflammation of sinonasal mucosa lasting more than 12 weeks.[6] Much ongoing research is being directed toward investigation of the underlying cause of CRS.[6-8] Current understanding supports inflammation, rather than infection, as the dominant causative factor.[6-8,10] A key issue in the pathogenesis of CRS is the maintenance of a patent osteomeatal complex, a functional unit that comprises the maxillary sinus ostia, anterior ethmoid cells and their ostia, ethmoid infundibulum, hiatus semilunaris, and middle meatus.[7,8] Therefore, older concepts for the development of CRS suggest that obstruction of the osteomeatal complex results in mucus stasis and changes in pH or luminal gas concentrations, thereby contributing to subsequent chronic bacterial infection with irreversible pathologic tissue changes in the sinus mucosa.[7,8] A recent review of studies showed that intrinsic and extrinsic factors, including staphylococcal colonization with superantigen elaboration, atopy, biofilm, and defective innate immunity, may participate in the complex interplay between the innate and adaptive immune systems, promoting the inflammation of sinus mucosa.[10-14]

CRS is classified as CRS with nasal polyps (CRSwNP) and without polyps (CRSsNP).[15] Recent research has demonstrated that the pathologies of CRSsNP and CRSwNP can be differentiated into distinct subgroups on the basis of the expression of inflammatory mediators and histopathological characteristics.[15] CRSwNP is associated with high tissue eosinophilia and increased Th2 cytokine expression. CRSwNP reveals frequent epithelial damage, a thickened basement membrane, and mostly edematous to sometimes fibrotic stromal tissue. In contrast, CRSsNP has more Th1 cytokine expression and less eosinophilic infiltration. On histopatholgocial examination, the mucosal lining in CRSsNP is characterized by basement membrane thickening, goblet cell hyperplasia, limited subepithelial edema, prominent fibrosis, and predominant infiltration of neutrophils.[15]

Because of the heterogenous nature of CRS, multiple medical therapies, including antibiotics, saline irrigations, and topical and systemic glucocorticoids, are widely advocated to achieve successful management.[5,16] Topical corticosteroids tend to constitute the first-line therapy in the medical management of CRS,

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and act by reducing sinus inflammation, and improving symptoms associated with CRS.[7,16] The efficacy of intranasal corticosteroids in treating patients with CRSsNP has been less clear, largely because of small study size and limitation of trial designs. Because long-term use of intranasal corticosteroids does not have adverse effects, topical corticosteroids are recommended for the treatment of CRSsNP owing to their anti-inflammatory effects.[17-21] Initial therapy in CRSwNP is intranasal corticosteroids, with the addition of oral steroids in symptomatic patients.[17-21] Preoperative and postoperative use of topical or systemic steroids has been shown to result in good success rates.[22-24] Topical steroids are beneficial in reduction of polyp size and prevention of polyp recurrence after endoscopic sinus surgery.[25] Furthermore, drug eluting middle meatal spacers have been developed to deliver topical corticosteroid therapy without the need for spray, drop, or irrigation delivery techniques, and have been shown to reduce the recurrence of sinonasal inflammation.[26-30]

There have been major advances in understanding molecular mechanisms that glucocorticoids suppress inflammation in CRS.[31] Glucocorticoids activate many anti-inflammatory genes and repress many proinflammatory genes that have been activated in inflammation as well as having several posttranscriptional effects.[32] Actually, a number of studies have demonstrated that the topical and systemic use of glucocorticoids inhibit the epithelial cell derived gene expression of numerous cytokines, including IL-1β, IL-6, and TNF-α, growth factor and receptors, such as GM-CSF and TGF-β, and numerous chemokines of the CXC and CC families.[31,32]

The anti-inflammatory effects of glucocorticoids in the airways are exerted through the glucocorticoid receptor (GR). Two GR isoforms exists, GRα and GRβ, which are derived from alternative splicing of GR primary mRNA. GRα is the classical GR that mediates glucocorticoid action, whereas GRβ is unable to bind steroids. GRβ alone is not transcriptionally active in AP-1or NF-κB driven systems. When overexpressed with respect to GRα, GRβ acts as a dominant-negative inhibitor of GRα transactivational activity.[31,32] A number of studies have revealed the expression levels of GRα and GRβ in nasal polyps and nasal mucosa, but their results are inconsistent.[33-38] Choi *et al.*[33] have reported that GRα mRNA is more expressed in nasal polyps than in normal nasal mucosa and that the elevated GRα mRNA levels are decreased after glucocorticoid treatment. GRβ mRNA expression is very low in NPs and nasal mucosa, and expression levels were similarly expressed regardless of glucocorticoid efficacy, indicating no correlation between the glucocorticoid sensitivity and the expression levels of GRβ mRNA. In accordance with these results, other research has shown that the prominent expression of GRα mRNA in NPs is decreased following glucocorticoid treatment, while GRβ mRNA expression remains unchanged. Taken together, these results suggest that GRα may play a major role in inflammation associated with NPs.[34] In contrast, another study has shown that GRβ mRNA is highly expressed in NPs and that down-regulation of GRα mRNA is found in glucocorticoid insensitive nasal polyps, suggesting that GRβ expression may play an important role in glucocorticoid therapy in nasal polyps.[35] Furthermore, in eosinophilic CRS, the number of GRβ-positive cells was increased in compared to non-eosinophilic groups, supporting the association with steroid insensitivity.[36] Pujols *et al.*[37] have reported that GRα is found in nasal mucosa and NPs and that its mRNA was lower in NPs than in nasal mucosa. GRβ is expressed at very low levels and does not significantly differ between nasal mucosa and NPs. They suggested that neither GRα nor GRβ appears to determine the sensitivity to glucocorticoids in NPs.[37] In epithelial cells derived from nasal mucosa and NPs, there is no difference in GRα mRNA expression, but GRα mRNA expression is more abundant than GRα mRNA expression in both nasal mucosa and NP epithelial cells.[38] Further studies to analyze GR in CRS are warranted.

The biological activity of glucocorticoids depends not only on the number of receptors and the dose and responsiveness of the target tissues or cells but also on the local metabolism of glucocorticoids catalyzed by 11β-hydroxysteroid dehydrogenase (11β-HSD).[39-41] Similar to exogenously administered glucocorticoids, endogenous glucocorticoids have been importantly implicated in inhibiting inflammatory responses in various organs.[42-45] Endogenous glucocorticoids are powerful modulators of inflammatory responses whose overall effects may result not only from circulating glucocorticoids via the hypothalamic-pituitary-adrenal axis, but also via tissue-specific metabolism of glucocorticoids catalyzed by 2 isoforms of 11β-HSD.[41]

The 2 isoforms of 11β-HSD, 11β-HSD1, and 11β-HSD2, modulate endogenous glucocorticoid action within cells and tissues at the prereceptor level. The 11β-HSD1 acts as an oxoreductase, generating active cortisol from cortisone, which potentiates the actions of glucocorticoids in tissues, whereas 11β-HSD2 inactivates cortisol to cortisone. Therefore, 11β-HSD1, increases the local concentration of active glucocorticoids, and 11β-HSD2 decreases the concentration, regulating local glucocorticoid concentrations.[41]

Traditionally, it was thought that glucocorticoids were solely synthesized in the adrenal cortex. However, a growing body of evidence has demonstrated *de novo* synthesis of glucocorticoids in other organs, such as the thymus, brain, skin, and vascular endothelium.[46] Other tissues, such as lung and intestinal epithelium, have been described to express steroidogenic enzymes, including CYP11B1, and are considered potential extra-adrenal sources of glucocorticoids.[47]

A recent study has shown that steroid converting enzymes and steroid synthesizing enzymes are expressed in human sinonasal mucosa. The results showed that the expression levels of 11β-HSD1 and CYP11B1 increased significantly in inflammatory sinus mucosa of patients with CRSwNP and CRSsNP,

compared with normal sinus mucosa.[48] However, 11β-HSD2 expression is decreased in inflammatory sinus mucosa, irrespective of the presence or absence of nasal polyps. CYP11A1 is also present in normal sinus mucosa, but its expression levels were unchanged in inflammatory sinus mucosa.[48] The expression of 11β-HSD1, 11β-HSD2, CYP11B1, and CYP11A1 is also detected in cultured epithelial cells obtained from human sinus mucosa.[48] In normal and inflammatory sinus mucosa these enzymes are similarly located in the superficial epithelium, submucosal glands, and vascular endothelial cells.[48] Expression levels of 11β-HSD1 and CYP11B1 are increased after stimulation with IL-4, IL-5, IL-1β, IL-13, TNF-α, and TGF-β1 compared to non-treated controls. In contrast, expression levels of 11β-HSD2 are decreased after treatment with IL-4, IL-5, IL-1β, IL-13, TNF-α, and TGF-β1. IFN-γ has no effect on the expression levels of these enzymes, and CYP11A1 expression levels are not affected by stimulation of these cytokines.[48]

Cortisol levels in the sinus mucosa and nasal lavage fluid are increased significantly in CRS patients, irrespective of the presence of polyps, compared to normal subjects. However, cortisol levels in the serum are unchanged in CRS patients compared to normal controls. In cultured epithelial cells stimulated with dexamethasone, expression levels of 11β-HSD1 are increased, compared to non-treated controls, whereas expression levels of 11β-HSD2 are decreased.[48] Taken together, these results suggest that reciprocal expression of 11β-HSD1 and 11β-HSD2 in the inflammatory sinus mucosa of patients with CRSwNP and CRSsNP may play an important role in the pathogenesis of CRS, contributing to the increased local supply of glucocorticoids. Nevertheless, more comparable studies on these issues are warranted.

In conclusion, there is now a preponderance of evidence supporting the concept that inflammation, as opposed to infection, is the dominant causative factor in CRS. Therefore, while systemic antibiotics were the mainstay of treatment in the past, the focus is now shifting toward novel anti-inflammatory therapies. In this respect, glucocorticoids have been used as anti-inflammatory agents for a long time. Understanding molecular mechanisms underlying the biological and pharmacological effects of glucocorticoids in CRS will aid in the treatment of CRS patients.

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