MUCOSAL CHANGES IN RHINITIS MEDICAMENTOSA

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To evaluate the nasal mucosal changes in rhinitis medicamentosa (RM), especially those related to goblet cells and subepithelial glands, we studied specimens of the inferior turbinate mucosa from 8 patients with RM, 8 patients with chronic hypertrophic rhinitis (CHR), and 5 patients with normal nasal mucosa. All specimens were assessed by electron microscopy and immunohistochemical study. Under a scanning electron microscope, hyperplasia of goblet cells was most prominent in the RM group, and an increased number of gland openings was evident in the RM and CHR groups. In addition, the immunoreactivity of epithelial growth factor receptor staining was strongest in the hyperplastic epithelium of the RM group. According to our results, it is feasible that the mucosa of patients with RM is in a chronic inflammatory, hypersecretory state. Degenerative changes in the secretary elements may cause impairment of mucociliary transport and may be responsible for the nasal obstruction and posterior nasal drip in RM.

KEY WORDS — epithelial growth factor receptor, rhinitis medicamentosa, scanning electron microscope.

INTRODUCTION

Nasal obstruction is one of the most common symptoms encountered in the field of rhinology. Frequent self-medication with decongestant nasal drops is often practiced by patients to relieve nasal obstruction. The misuse or abuse of these topical medications has injurious effects on the nasal mucosa, such as metaplasia, dilatation, and engorgement of the subepithelial blood vessels. Topical nasal decongestants include 2 classes of drugs: sympathomimetic amines (e.g., phenylephrine) and imidazoles (e.g., oxymetazoline). The imidazoles appear more likely to cause rebound congestion and rhinitis medicamentosa (RM) than are the sympathomimetic amines, possibly because of their longer duration of effect and their action on mucosal blood flow. Histopathologic studies in animals have shown squamous metaplasia with loss of cilia and fibrosis, goblet cell hyperplasia, edema of the corium, mononuclear cellular infiltration, and glandular hyperplasia. There are few detailed data regarding the transformation of mucosal secretory elements in RM, especially in humans.

In this study, we attempted to evaluate the epithelial changes, especially focusing on goblet cells and subepithelial glands, in RM in order to gain deeper insight into its pathogenesis.

MATERIALS AND METHODS

Specimens of the inferior turbinate mucosa from 8 patients with RM and 8 patients with chronic hypertrophic rhinitis (CHR) were included in this study. Normal nasal mucosal specimens taken from 5 patients who were undergoing nasopharyngeal biopsy or traumatic surgery were evaluated as a control. The patients with RM all had a history of nasal obstruction, overuse of nasal decongestants for at least 3 months, and a poor response to local decongestion.

Fig 1. Nasal mucosa of patient with rhinitis medicamentosa, illustrated under scanning electron microscopy (original x1,000). Loss of cilia, epithelial degenerative changes, and hyperplasia of goblet cells are noted.

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agents. All specimens from the patients with RM and CHR were taken during turbinectomy. Specimens were separated into 2 parts: one for electron microscopic study and the other for immunohistochemical study.

The specimens for electron microscopic study were fixed with 2% glutaraldehyde, postfixed with 2% osmium tetroxide, dehydrated with an alcohol series, and critical-point-dried. After sputter-coating with gold, the surface of the specimen was analyzed under a Hitachi-600 scanning electron microscope, with special attention being paid to the distribution of goblet cells and gland openings. The goblet cells were counted, and the number was expressed as a percentage of the total number of epithelial cells. At least 500 cells were counted by scanning electron microscopy (SEM; at a magnification of ×2,000). Gland openings were counted in 15 visual fields by SEM (×2,000). Every specimen was counted 10 times to yield each score. Student's t-test and 95% confidence intervals were used for comparisons among groups.

The specimens for immunohistochemical study were fixed in paraffin sections. The paraffin sections were thinly sliced (4-μm thickness) and mounted on polylysine-coated glass slides. After deparaffinization and rehydration, the slides were treated in a microwave oven for antigen retrieval. Endogenous peroxidase was inhibited by immersing slides in 3% hydrogen peroxide for 10 minutes. To avoid nonspecific binding, we incubated the slides with 10% goat serum for 60 minutes. The slides were washed with phosphate-buffered saline solution (PBS) and incubated with monoclonal antibody to EGFR (epidermal growth factor receptor; dilution: 1:100; Dako, Glostrup, Denmark) overnight at 4°C. After rinsing with PBS, the slides were incubated with biotinylated goat anti-rabbit immunoglobulin G (Dako) at room temperature for 15 minutes. The slides were then washed with PBS and treated with streptavidin-horseradish peroxidase reagent (Dako) at room temperature for 15 minutes. After washing with PBS, the activity of peroxidase was detected with an AEC substrate kit (Zymed, South San Francisco, California), and then the slides were counterstained with hematoxylin. A negative control was formed by omitting

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**Fig 2.** Strong immunoreactivity to epidermal growth factor receptor (EGFR) is shown in most of nasal mucosa from subject with rhinitis medicamentosa. Immunopositive cells (arrows) are prominent in basal layers of hyperplastic epithelium.
TABLE 2. EGFR AND PAS/AB IMMUNOHISTOCHEMICAL STAINING OF HUMAN NASAL MUCOSA

<table>
<thead>
<tr>
<th>Group</th>
<th>EGFR</th>
<th>PAS/AB</th>
<th>EGFR</th>
<th>PAS/AB</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHR</td>
<td>Moderate to weak</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>RM</td>
<td>Strong to moderate</td>
<td>Strong to moderate</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Normal</td>
<td>Weak to negative</td>
<td>Weak to negative</td>
<td>Weak to negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

EGFR — epithelial growth factor receptor; PAS/AB — periodic acid-Schiff-Alcian blue stain.

The primary antibody.

The surface epithelium of the nasal mucosa presented various morphological subtypes: 1) normal pseudostratified epithelium (composed of ciliated cells, goblet cells, and a single layer of basal cells); 2) hyperplastic epithelium consisting of ciliated cells and basal and goblet cells (containing more than 3 cell layers of basal cells, mucous cells, or both); and 3) epithelial damage or portions with squamous metaplasia. Areas of squamous metaplasia and damage were excluded from the analysis. We determined the areas of pseudostratified and hyperplastic epithelium in each specimen. There were large differences among the different specimens. Evaluation of EGFR immunoreactivity was assessed by a double-checking method in 20 high-power fields (x200). The reactivity of staining was expressed arbitrarily as negative, weak, moderate, or strong.

RESULTS

The nasal epithelium of the CHR and RM groups showed severe hyperplasia, loss of cilia, and increased numbers of goblet cells and submucosal glands under SEM (Fig 1). Hyperplasia of goblet cells was more prominent in the RM group than in the CHR and normal groups. The number of gland openings was increased in the RM and CHR groups as compared to the normal control group (Table 1). The immunoreactivity to EGFR was strongest in the hyperplastic epithelium of RM subjects (Fig 2; Table 2). There was moderate EGFR-positive staining in the CHR group (Fig 3), and weak staining in the normal group (Fig 4).

DISCUSSION

The term rhinitis medicamentosa can be traced back to 1946 and was coined by Lake. It represents nasal obstruction as a rebound phenomenon caused by misuse or overuse of topical decongestant nasal drops and the disappearance of their decongestive effect. We were unable to make a diagnosis of RM solely on the basis of a patient's having nasal obstruction combined with a history of nasal vasoconstrictor overuse, because other causes can account for nasal obstruction. In order for the diagnosis to be convincing, the characteristic nasal mucosal changes plus a poor response to local sympathomimetic agents had to be present. Our RM patients were chosen accordingly.

The nasal epithelia of the RM and CHR groups exhibited severe hyperplasia, loss of cilia, and increased numbers of goblet cells and submucosal glands. In addition, there was a prominent increase in the number of goblet cells in the RM group as compared to both the CHR and normal groups. Currently, we do not completely understand why the mucosa of RM showed a greater increase in the number of goblet cells and glands.
cells and submucosal glands. Either RM may be directly caused by mucosal changes from the topical nasal decongestants, or a specific condition may occur after abuse of these drops that then produces these morphological changes. Thus, more proof is required to identify which factors cause the mucosal changes in RM.

Epidermal growth factor receptor, a 70 kd membrane glycoprotein, is expressed in fetal airways, in which it plays an important role in epithelial cell differentiation, cell proliferation, and branching morphogenesis. However, in healthy adult human airways, EGFR is rarely expressed except in malignant tumors and hypersecretory airway disease. The expression of EGFR is the essential mechanism for producing mucus in goblet cells. In our study, immunoreactivity to EGFR was stronger in the hyperplastic epithelium of the RM group than in the other two groups. Thus, we noted cells positively stained for EGFR and hyperplasia of goblet cells in the RM group. This finding suggests a special relationship between EGFR expression and hyperplasia of goblet cells. At the same time, it documents that EGFR expression in the airway epithelium is mediated by EGFR activation. This result is compatible with findings of previous articles.13,14

Although the epithelia of the upper and lower airways of healthy human beings contain some goblet cells, they do not normally express EGFR. Among our normal specimens, the immunoreactivity to EGFR was weak to negative, representing a noninflammatory condition in the epithelium. In contrast, the upregulation of EGFR in epithelial cells of the RM group indicated a chronic inflammatory hypersecretory state.

Indeed, the expression and activation of EGFR may be prerequisites for an inflammatory state.15 Rebound nasal congestion in RM indicates increased vascular permeability, and mononuclear cells may be recruited as described in histopathological studies of animals. Therefore, a true chronic inflammatory condition is present in RM, as is compatible with the finding of upregulated EGFR in this study.

Moreover, an increased number of submucosal glands was found in the nasal epithelium of the RM group in our study. This finding is further evidence that the RM mucosa is in a chronic inflammatory state. These additional submucosal glands may produce an abnormal mucus blanket or a tethering phenomenon that may be harmful to the defense mechanisms of the mucosa. Thus, it is feasible that the mucosa of RM is in a chronic inflammatory condition and that a vicious cycle ensues, according to our immunohistochemical and electron microscopic results.

As is known, secretory elements such as goblet cell density and submucosal gland number may provide evidence of pathological conditions. In turn, degenerative changes in the secretory elements may cause impaired mucociliary transport. Especially in the RM group, a hypersecretory state of the goblet cells, combined with such morphological changes as secretory elements in the mucosa, was apparent from our results. Therefore, in addition to rebound congestion, these characteristic mucosal changes may contribute to the clinical symptoms of nasal obstruction and posterior nasal drip in persons with RM.
REFERENCES