Stimulatory effects of histamine on migration of nasal fibroblasts

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Abstract

Background:
Fibroblast migration is crucial for normal wound repair after sinonasal surgery. Histamine is known to be involved in wound healing by its effects on cell proliferation and migration. This study aimed to determine whether histamine affects the migration of nasal fibroblasts and to investigate the mechanism of action of histamine on nasal fibroblasts.

Methods:
Primary cultures of nasal fibroblasts were established from inferior turbinate samples. Fibroblast migration was evaluated with scratch assays. Cells were treated with histamine and/or histamine receptor-selective antagonists. U-73122 and pertussis toxin, which are selective inhibitors of the lower signaling pathway of H1R and H4R, were used to confirm the modulation of nasal fibroblast migration by histamine. Fibroblast cytoskeletal structures were visualized with immunocytochemistry.

Results:
Histamine significantly stimulated the migration of nasal fibroblasts. Antagonists selective for HR1 and HR4 significantly reduced nasal fibroblast migration. In immunocytochemical staining, histamine treatment increased membrane ruffling and pyrilamine, diphenhydramine, fexofenadine, and JNJ777120 decreased histamine-induced membrane ruffling. U-73122 and pertussis toxin also decreased histamine-induced migration of fibroblasts.

Conclusion:
We showed that histamine stimulates fibroblast migration in nasal fibroblasts. This effect appeared to be mediated by HR1 and HR4.

Introduction

The postoperative healing of sinonasal mucosa wounds is a highly organized process with a well-regulated sequence of events, including cell migration and proliferation, coagulation, reepithelialization, inflammation, extracellular matrix (ECM) deposition, cell–cell adhesion, and cell–matrix interactions.

Originally, histamine was considered one of the major inflammatory mediators in allergy, because it is released from mast cells in the immediate-phase and basophils in the late-phase response, and induces most of the symptoms of allergic rhinitis, including itching, sneezing, rhinorrhea, and nasal obstruction. In addition to its classical roles as an inflammatory mediator, histamine is also involved in cell proliferation and differentiation, hematopoiesis, embryonic development, tissue regeneration, and wound healing. It is generally accepted that histamine plays an important role both in normal physiology as well as in various pathologies.

This study aimed to determine whether histamine affects the migration of nasal fibroblasts and to investigate the mechanism of action of histamine on nasal fibroblasts.

Materials and Methods

Inferior turbinate mucosa specimens were obtained from six patients during endoscopic sinus surgery for benign tumors. Primary cultures of nasal fibroblasts were established from inferior turbinate samples. Fibroblasts in the fourth cell passage were used. Fibroblast migration was evaluated with scratch assays. Cells were treated with histamine and/or histamine receptor-selective antagonists. U-73122 and pertussis toxin, which are selective inhibitors of the lower signaling pathway of H1R and H4R, were used to confirm the modulation of nasal fibroblast migration by histamine. And fibroblast cytoskeletal structures were visualized with immunocytochemistry. Statistically significant differences between groups were assessed by one-way ANOVA for factorial comparisons and Tukey’s test for multiple comparisons. A value of $p < 0.05$ was accepted as significant.

Results

Fig. 1.Cytotoxicity of histamine determined by MTT assay. MTT = 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide.

Fig. 2. Effects of histamine on nasal fibroblast migration in wound scratch assays.

Fig. 3. Effects of histamine receptor antagonists on migration of histamine-treated nasal fibroblasts.

Fig. 4. Effects of blocking Y2R and H4R signaling on migration of histamine-treated nasal fibroblasts.

Fig. 5. Effect of mitomycin C on migration of histamine-treated nasal fibroblasts.

Conclusions

We showed that histamine stimulates the migration of nasal fibroblasts, and that this effect appears to be mediated by HR1 and HR4. Thus, the present study provides evidence for the suppressive effects of antihistamines, especially, selective H1 receptor antagonists, on fibroblast migration, which is important in surgical wound healing.

However, fibroblast migration also can be involved in scarring and fibrosis that have deleterious effects on in some types of chronic rhinosinusitis. So more research is necessary to determine the effects of antihistamine on wound healing after sinus surgery.

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