INTRODUCTION

Histamine is a major chemical mediator that induces nasal allergy symptoms through its binding to histamine H1 receptor (H1R) in the development of allergic rhinitis (1). Antihistamines, H1R antagonists, are effective for the treatments of allergic rhinitis, including pollinosis (2). In Japan, prophylactic administration of antihistamines before the onset of pollen season is recommended for pollinosis treatment (1), because the pre-seasonal administration of antihistamines is more effective than post-onset administration in patients with pollinosis (3). In our previous study, we used environmental exposure units and demonstrated that pre-administration of ebastine, an antihistamine down-regulated H1R gene expression before pollen exposure and then inhibited pollen-induced nasal symptoms and pollen-induced up-regulation of H1R gene expression in the nasal mucosa of patients with pollinosis (4). Because, histamine signaling is regulated by the levels of H1R expression (5, 6), it is suggested that prophylactic administration of antihistamines inhibited both basal transcription and histamine-induced transcriptional activation of H1R in the nasal mucosa, resulting in summative suppression of nasal symptoms during peak pollen season in patients with pollinosis.

Intranasal corticosteroid (INCS) is also effective for the treatment of allergic rhinitis (7). A recent randomized placebo-controlled trial demonstrated that pre-seasonal prophylactic administration of INCS prevented the worsening of nasal symptoms during peak pollen season in patients with pollinosis (8). Accordingly, in the present study, we examined whether INCS down-regulates H1R gene expression in the nasal mucosa of healthy participants in vivo. We then examined whether dexamethasone, a corticosteroid inhibits basal and histamine-induced up-regulation of H1R mRNA, and histamine-induced phosphorylation of protein kinase Cδ (PKCδ) and extracellular signal-regulated kinase (ERK) in HeLa cells in vitro.

PARTICIPANTS AND METHODS

Participants

We enrolled 16 healthy participants with no history of allergic rhinitis (10 males, 6 females; 22-26 years old; mean age: 24.2 years). Participants received intranasal doses of 200 µg of mometasone furoate in the right nostril using a nasal spray device once daily for a week. Nasal mucosa samples were obtained under local anesthesia with 4% lidocaine by scraping the surface of the inferior nasal concha with a small spatula before and after INCS administration for 7 days, as previously described (6). This study was approved by the Ethical Committee of Tokushima University Hospital (UMIN0694), and written informed consent was obtained from each patient before inclusion in the study.

Real-time quantitative RT-PCR

Nasal mucosa samples of participants were frozen in RNAlater® (Applied Biosystems, Foster City, CA, USA) and stored at -80°C until use. Total RNA was isolated using the RNAsqueen-Micro Kit (Applied Biosystems) following the manufacturer's instructions. RNA samples were reversed-transcribed to produce cDNA using a High Capacity cDNA Reverse Transcription Kit (Applied Biosystems). The levels of H1R mRNA in the nasal mucosa of healthy participants receiving INCS was significantly decreased. Dexamethasone suppressed basal levels of H1R mRNA, and histamine-induced up-regulation of H1R mRNA and ERK phosphorylation in HeLa cells. These data suggested that corticosteroid inhibited both basal transcription and histamine-induced transcriptional activation of H1R through its suppression of ERK phosphorylation in the signaling pathway involved in H1R gene transcription. It is further suggested that pre-seasonal prophylactic administration of INCS suppresses both basal and pollen-induced upregulation of H1R gene expression in the nasal mucosa of patients with pollinosis, leading to prevention of the exacerbation of nasal symptoms during peak pollen season.

Abstract: The purpose of this study is to examine the effect of intranasal corticosteroid (INCS) administration on histamine H1 receptor (H1R) gene expression in the nasal mucosa of healthy participants and the effects of dexamethasone on basal and histamine-induced H1R mRNA expression, and histamine-induced phosphorylation of extracellular signal-regulated kinase (ERK) in HeLa cells. Sixteen healthy participants were given INCS once daily for a week. After pretreatment of dexamethasone, HeLa cells were treated with histamine. Levels of H1R mRNA and phosphorylation of ERK were measured using real time PCR and immunoblot analysis, respectively. Levels of H1R mRNA in the nasal mucosa of healthy participants receiving INCS was significantly decreased. Dexamethasone suppressed basal levels of H1R mRNA, and histamine-induced up-regulation of H1R mRNA and ERK phosphorylation in HeLa cells. These data suggested that corticosteroid inhibited both basal transcription and histamine-induced transcriptional activation of H1R through its suppression of ERK phosphorylation in the signaling pathway involved in H1R gene transcription. It is further suggested that pre-seasonal prophylactic administration of INCS suppresses both basal and pollen-induced upregulation of H1R gene expression in the nasal mucosa of patients with pollinosis, leading to prevention of the exacerbation of nasal symptoms during peak pollen season.

Keywords: corticosteroids, extracellular signal-regulated kinase, healthy participants, histamine H1 receptor, intranasal administration

Received for publication May 17, 2020; accepted June 14, 2020.
Address correspondence and reprint requests to Yoshiaki Kitamura, Department of Otolaryngology, Institute of Biomedical Sciences, Tokushima University Graduate School, 3-18-15 Kuramoto, Tokushima 770-8503, Japan and Fax: +81-88-633-7170.
RESULTS

Effect of INCS administration on H1R mRNA levels in the nasal mucosa of healthy participants.

Levels of H1R mRNA in the nasal mucosa of healthy participants receiving INCS once a day for a week were significantly decreased, compared to those before INCS administration (Fig. 1). No localized adverse events, such as nasal burning or epistaxis, were observed.
inflammation and eosinophil migration in the nasal mucosa of patients with allergic rhinitis (15).

In the present study, we showed that dexamethasone also suppressed histamine-induced up-regulated H1R gene expression in HeLa cells, as reported previously (10). We also showed that immunoblot analysis showed that dexamethasone suppressed histamine-induced ERK phosphorylation, but not PKCδ phosphorylation in HeLa cells. The PKCδ/ERK/poly (ADP-ribose) polymerase-1 (PARP-1) signaling pathway was involved in histamine-induced up-regulation of H1R gene expression in HeLa cells after PKCδ and ERK activation by phosphorylation (11). Therefore, it is suggested that ERK is a target molecule of dexamethasone to suppress transcriptional activation of H1R.

Because we previously showed that corticosteroids suppressed histamine-induced transcriptional activation of H1R in the nasal mucosa of a rat model of allergic rhinitis (16), it is assumed that INCS would suppress histamine-induced up-regulation of H1R in the nasal mucosa of patients with pollinosis. Although the hypothesis should be proved in the further study, the findings in the present study suggest that prophylactic administration of INCS before pollen dispersion suppresses transcriptional activation of H1R, as well as its basal transcription in the nasal mucosa, resulting in the prevention of worsening of nasal symptom during peak pollen season in patients with pollinosis.

In conclusion, we showed INCS down-regulated H1R gene expression in the nasal mucosa of healthy participants with no history of allergic rhinitis. We also showed that dexamethasone, a corticosteroid inhibited basal transcription and transcriptional activation of H1R in HeLa cells through its suppression of ERK phosphorylation in the PKCδ/ERK/PARP-1 signaling involved in H1R gene transcription. These data suggest that pre-seasonal prophylactic administration of INCS suppresses both basal and pollen-induced up-regulation of H1R gene expression in the nasal mucosa of the patients with pollinosis, leading to prevention of the exacerbation of nasal symptoms during peak pollen season.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

ACKNOWLEDGEMENTS

This work was financially supported in part by Grant-in-Aid for the Japan society for the Promotion of Science, and from the Osaka Medical Research Foundation for Intractable Diseases. This study was supported by Support Center for Advanced
AUTHORS CONTRIBUTION

YK and HM designed the study and wrote the manuscript. SK and TF carried out experimental work. KN, EK, KM, TA, and GS contributed to data collection and interpretation of results. HF and NT supervised the research and wrote the manuscript. All authors read and approved the final manuscript.

REFERENCES


