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Histamine H4 receptor regulates Th2-cytokine profile through thymic stromal lymphopoietin in allergic rhinitis

Wei Wei Wang[1] · Yong Liang Pan[1] · Hong Wei Yu[1] · Bo Zhang[1] · Sheng Wen Shao[1]

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Abstract

Purpose Epithelial thymic stromal lymphopoietin (TSLP) promotes Th2 inflammatory responses through induction of OX40 ligand (OX40L) on dendritic cells in allergic rhinitis (AR). Emerging evidence supports the important role of histamine H4 receptor (H4R) in allergic inflammation. This study aimed to investigate the effects of H4R in Th2-cytokine profile mediated by TSLP in AR.

Methods Human nasal epithelial cells (HNECs) from AR patients were stimulated with histamine in the presence or absence of H4R agonist (4-methylhistamine, 4-MH) and antagonist (NJ7777120, JNJ) or H1R agonist (2-pyridylethylamine). TSLP protein was measured by Western blotting and ELISA. To further elucidate the role of H4R in the in vivo situation of experimental AR, rats were sensitized and treated with JNJ or 4-MH. TSLP and OX40 ligand (OX40L) in the nasal mucosa were assayed by Western blotting. Th2 cytokines including interleukin-4, 5 and 13 in nasal lavage fluids were detected by ELISA.

Results Histamine alone did not induce TSLP production by HNECs. The pre-incubation with 4-MH prior to histamine promoted TSLP expression, which was inhibited by the stimulation with JNJ prior to histamine and 4-MH. The pre-incubation with 2-pyridylethylamine before histamine stimulation had no impact on TSLP production. In AR rats, the levels of TSLP and OX40L protein were increased as well as Th2 cytokines, which was further up-regulated by 4-MH treatment, while JNJ treatment attenuated these effects.

Conclusions H4R activation induced TSLP production by HNECs, which up-regulated OX40L expression in the nasal mucosa of sensitized rats. These factors promoted Th2-cytokine profile in AR.

Keywords Allergic rhinitis · Human nasal epithelial cells · Thymic stromal lymphopoietin · Histamine H4 receptor · OX40 ligand · Th2 immune response

Introduction

Allergic rhinitis (AR) is a chronic inflammatory disease with a prevalence of about 10–50% [1]. AR is mainly caused by Th2 immune responses in the upper airway characterized by the induction of Th2 cytokines including interleukin (IL)-4, 5 and 13 released by Th2 cells and immunoglobulin E (IgE) production against foreign protein [2–5]. During this process, the main effector mechanism that induces Th2 polarization is the presentation of allergens recognized by dendritic cells (DCs) to naive $CD4^+$ T cells [5]. The differentiation of naive $CD4^+$ T cells depends on various costimulatory molecules on T cells and their cognate ligands on DCs. One of the critical costimulatory molecules is OX40 and OX40 ligand (OX40L) [6]. The interaction between OX40L and OX40 plays an essential role in T-cell polarization towards Th2 patterns [6, 7].

The recent concept that the epithelial barrier is fundamental to the onset of Th2 responses has been supported by the discovery of thymic stromal lymphopoietin (TSLP) [8]. TSLP, an IL-7-like cytokine, is released by epithelial cells at a barrier such as airway and skin in response to danger signals [9]. Increased TSLP is observed in allergic tissues such as nasal mucosa of AR, lung of asthmatics and lesional skin of atopic dermatitis (AD), which is implicated as a key molecule for initiating allergic inflammation at the interface between DCs and epithelial cells [10]. DCs are activated by TSLP prime naive $CD4^+$ T cells to differentiate into Th2

✉ Sheng Wen Shao
shaoswzhejiang@163.com

[1] Schools of Medicine and Nursing Sciences, Huzhou University, No.759, East Second Ring Road, Huzhou 313000, Zhejiang, China

cells [11]. In this process, OX40L on DCs is preferentially induced by TSLP, leading to Th2 polarization [12, 13]. Hence, TSLP-mediated OX40L signaling induces aberrant Th2 response in allergic diseases.

The local release of histamine is recognized as an important step in hypersensitivity reactions to antigens [14]. Histamine mediates its effects via four G-protein-coupled receptors [15]. Histamine H1 receptor (H1R) is known to be the main receptor that mediates histamine effects in nasal allergy. H1R antagonists are shown to effectively relieve the symptoms of AR patients, and are used as first-line therapy for AR [16]. But H1R is not the sole contributor to allergic diseases because its antagonists have little or no efficacy in asthma [17]. Recently, histamine H4 receptor (H4R) has been identified as a potential modulator of DC activation and T-cell polarization, and has a distinct pharmacological profile from H1R [18], Proof for the efficacy of H4R antagonists or gene knockout in models of AR, asthma and AD highlights H4R in histamine-mediated effects [19].

Although current evidence supports the important role of H4R in Th2 priming capability of DCs [20, 21], whether H4R is involved in Th2 paradigm mediated by TSLP in AR is as yet unknown. We hypothesized that H4R was involved in Th2-mediated cascade triggered by TSLP. To test this hypothesis, we evaluated the in vitro effects of H4R on histamine-mediated TSLP production by human nasal epithelial cells (HNECs) from AR patients by comparison with H1R. Further investigation showed the regulatory mechanism of H4R on Th2-cytokine profile in the in vivo situation of experimental AR. The exact understanding of this mechanism would provide an insight into the biological effects of H4R underlying the Th2 immune responses in AR.

Materials and methods

The culture and stimulation of HNECs

This study was approved by the Institutional Review Board of Huzhou University. Written informed consents were obtained from the patients regarding the surgical operation and the use of resected specimens for research. The nasal mucosa tissues on the inferior turbinates were obtained from 36 patients who were diagnosed with AR complicated with turbinate hypertrophy in the Head and Neck Surgery Department of Huzhou Central Hospital. The ages of the patients ranged from 18 to 45 years old. They did not take systemic or local glucocorticoids, drugs that would inhibit cell growth, nor had they previously had a nasal operation or an external injury. The tissues were immediately placed in sterile saline after surgery, and were digested with 0.01% collagenase I (4A Biotech Co., Ltd, Beijing, China), and epithelial cells were harvested and cultured as previously described [22].

The confluent cells were stimulated for 24 h with histamine (100 μM; Tocris Bioscience, Bristol, United Kingdom), or the cells were pre-incubated with H4R agonist 4-methylhistamine (4-MH, 10 μM; Tocris Bioscience) or H1R agonist 2-pyridylethylamine (2-PyEA, 10 μM; Tocris Bioscience) for 24 h prior to histamine. H4R antagonist JNJ7777120 (JNJ, 10 μM; Tocris Bioscience) was added 1 h before H4R agonist. Control cells were treated with NS. Based on reported studies [23, 24], optimal concentrations for the medicines were chosen. The cells and supernatants were collected.

The protocol for the sensitization

The sensitization of animals was performed as previously reported [25, 26]. Sprague Dawley rats (Jiesijie Co., Ltd, Shanghai, China) were immunized with an intraperitoneal injection of 1 ml NS containing 0.3 mg ovalbumin (OVA; Sigma, St Louis, Missouri) and 300 mg aluminum hydroxide (Alum, $Al(OH)_3$; Sigma) once every other day. From day 14, 0.1 ml of NS containing 10 mg OVA was instilled into both nasal cavities of rat once a day for 7 days.

Grouping, treatment and sample collection

Rats whose weight ranged from 150 to 170 g were randomized into four groups: group control (group A, 12 rats), group model (group B, 12 rats), group treated with JNJ (group C, 12 rats) and group treated with 4-MH (group D, 12 rats). Groups B, C and D were sensitized according to the protocol above. Group A were treated with NS without OVA. Thirty minutes before intranasal challenge, JNJ or 4-MH (30 mg/kg) was intraperitoneally administered. Based on the reported study, the dosage of JNJ and 4-MH was chosen [27].

Rats were sacrificed with an intraperitoneal overdose of sodium pentobarbital (100 mg/kg, Sigma) 1 h after the last intranasal challenge. Before the nasal mucosa tissues were collected, an epidural anesthesia tube was placed and fixed into the nasal cavity at 2 cm. The rats were placed upside down, and the bilateral nasal cavities were lavaged with 1.5 ml NS. The nasal lavage fluids (NLF) was centrifuged at 3000 rpm/min for 15 min, and the supernatants were collected.

Western blotting

The protein from HNECs or nasal mucosa was extracted using radio-immunoprecipitation assay buffer (4A Biotech). After denaturation, equal amounts of protein from each sample were prepared for 12% sodium dodecyl sulfate gel

electrophoresis (Beyotime, Haimen, Jiangsu, China). Protein was transferred after electrophoresis to PVDF membranes (Beyotime). The membranes were blocked with blocking buffer (Beyotime), and were incubated with a 1:300 dilution of rabbit anti-TSLP antibody (4A Biotech), a 1:200 dilution of rabbit anti-OX40L antibody (4A Biotech) or a 1:1000 dilution of mouse anti-β-actin antibody (Beyotime). The membranes were then incubated with secondary antibody. Antibody binding was detected with Beyond ECL Plus (Beyotime). The density of the bands was analyzed using Quantity One software (Silk Scientific Corporation, Orem, UT).

ELISA

The contents of TSLP in cell supernatant and IL-4, 5 and 13 in NLF were analyzed using the ELISA kit (Westang biotech co., Ltd, Shanghai, China). The procedures were performed according to the manufacturer's instructions. Optical density values were measured at 450 nm by an ELISA plate reader (Bio-Rad, Hercules, California).

Statistical analysis

Results were analyzed using SPSSS 13.0 software (SPSS Inc, Chicago, IL). The data were expressed as mean ± SD. One-way analysis of variance (ANOVA) followed by post hoc analysis was used when appropriate. Difference was considered significant at P value less or equal to 0.05.

Results

As shown in Fig. 1, no difference was observed although the levels of TSLP protein in histamine-stimulated cells increased by 23.74% compared to control cells ($P > 0.05$). Its expression induced by 4-MH and histamine were up-regulated by 2.64-fold compared to histamine alone ($P < 0.05$). But a 54.33% decrease was observed in pre-treatment with JNJ prior to 4-MH and histamine compared to 4-MH and histamine ($P < 0.05$). When the cells were stimulated with H1R agonist 2-PyEA prior to histamine, TSLP expression was increased by 2.50% compared to histamine alone, while there was no difference ($P > 0.05$). From Fig. 2, there was no difference in the production of TSLP protein in cell supernatants between histamine-stimulated cells and control cells ($P > 0.05$). The pre-incubation with 4-MH prior to histamine up-regulated the levels of TSLP protein by 68.54% compared to histamine alone ($P < 0.05$). But, the stimulation with JNJ prior to 4-MH and histamine led to a 25.50% decrease of TSLP expression compared to 4-MH and histamine ($P < 0.05$). The stimulation with 2-PyEA prior to histamine increased the TSLP expression by 3.53% compared to histamine alone ($P > 0.05$). These results indicated that

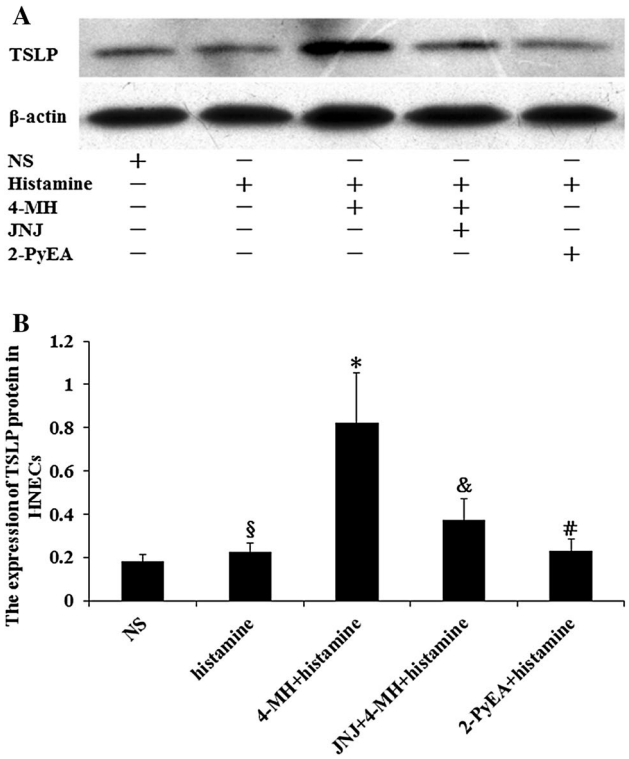

Fig. 1 Western blotting analysis of TSLP protein in HNEpCs. β-Actin was used as the loading control. The intensity of TSLP bands was normalized to the intensity of β-actin bands. "§" Represents $P > 0.05$ vs stimulation with NS, "*" represents $P < 0.05$ vs stimulation with histamine alone, "&" represents $P < 0.05$ vs stimulation with 4-MH and histamine, and "#" represents $P > 0.05$ vs stimulation with histamine alone

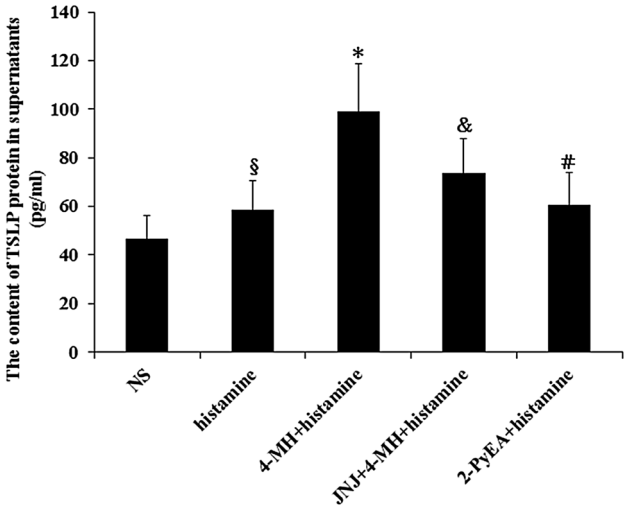

Fig. 2 ELISA assay for TSLP protein in cell supernatants. "§" Represents $P > 0.05$ vs stimulation with NS, "*" represents $P < 0.05$ vs stimulation with histamine alone, "&" represents $P < 0.05$ vs stimulation with 4-MH and histamine, and "#" represents $P > 0.05$ vs stimulation with histamine alone

only through H4R did histamine induce TSLP production by HNECs, while H1R was not involved in this process.

Figure 3 showed that the expression of TSLP protein in the nasal mucosa was increased by 2.08-fold in group B compared to group A ($P < 0.05$). While JNJ treatment in group C led to a 44.98% decrease of TSLP expression compared to that in group B ($P < 0.05$). After the rats in group D were treated with 4-MH, the level of TSLP protein was upregulated by 63.57% compared to that in group B ($P < 0.05$). We further assayed the effect of H4R on OX40L production (Fig. 4), finding that the expression of OX40L protein in group B was 4.44 times that in group A ($P < 0.05$), while its level in group C was reduced by 56.92% compared to that in group B ($P < 0.05$). The expression in group D treated with 4-MH was increased by 76.18% ($P < 0.05$). These data showed that H4R activated TSLP-OX40L signaling in AR.

From Fig. 5, we observed that IL-4 level in group B was significantly elevated by 1.26-fold compared with group A ($P < 0.05$). After the treatment with JNJ, IL-4 level in group C was markedly reduced by 34.31% compared with group B ($P < 0.05$), while the level in group D was significantly increased by 31.73% compared with group B ($P < 0.05$). IL-5 level in group B was 0.93-fold higher than that in group A ($P < 0.05$). Group C showed significantly lower IL-5 expression by 36.78% than group B ($P < 0.05$). IL-5 level in group D was increased by 39.60% compared with group B ($P < 0.05$). In group B, IL-13 was increased by 1.07-fold compared with group A. A 36.35% decrease of IL-13 expression was observed in group C compared with group B ($P < 0.05$). IL-13 level was significantly higher in group D by 41.36% compared with group B ($P < 0.05$). These results indicated that H4R enhanced the production of Th2 cytokines including IL-4, 5 and 13 in AR.

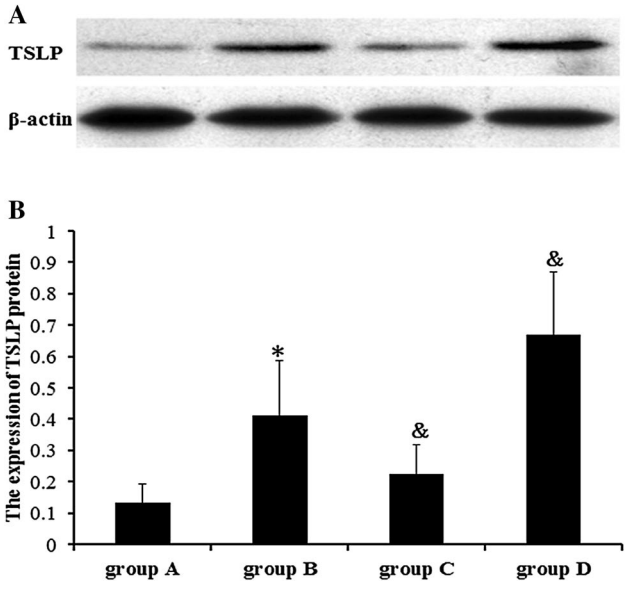

Fig. 3 Western blotting analysis of TSLP protein in the nasal mucosa. Group A were immunized with alum before NS challenge and treatment. Group B were immunized with OVA and alum before OVA challenge and NS treatment. Group C were immunized with OVA and alum before OVA challenge and JNJ treatment. Group D were immunized with OVA and alum before OVA challenge and were 4-MH treatment. β-actin was used as loading control. The intensity of TSLP bands was normalized to the intensity of β-actin bands. "*" Represents $P < 0.05$ vs group A, and "&" represents $P < 0.05$ vs group B

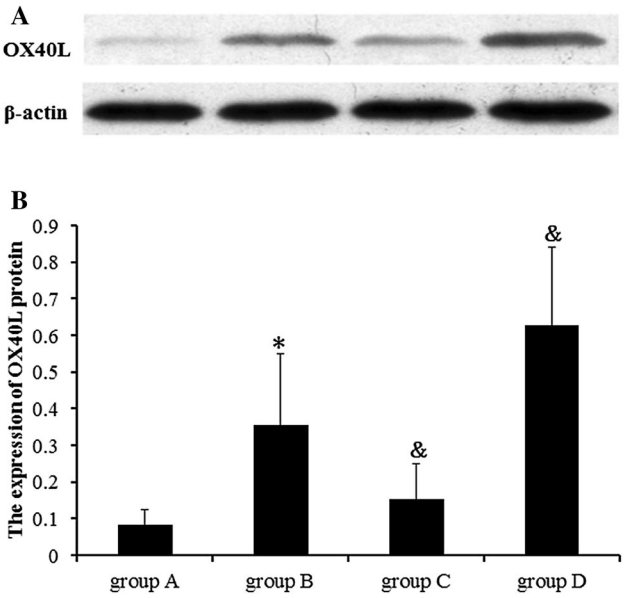

Fig. 4 Western blotting analysis of OX40L protein in the nasal mucosa. Group A were immunized with alum before NS challenge and treatment. Group B were immunized with OVA and alum before OVA challenge and NS treatment. Group C were immunized with OVA and alum before OVA challenge and JNJ treatment. Group D were immunized with OVA and alum before OVA challenge and were 4-MH treatment. β-actin was used as loading control. β-actin was used as loading control. The intensity of OX40L bands was normalized to the intensity of β-actin bands. "*" Represents $P < 0.05$ vs group A, and "&" represents $P < 0.05$ vs group B

Discussion

Epithelial cells have the capacity to produce inflammatory cytokines that play a critical role in promoting tissue inflammation [24, 28]. Both H1R and H4R are found in normal airway epithelial cells [29, 30], but H4R expression was faint [31]. They are significantly increased in nasal epithelial cells during inflammatory conditions [30]. Histamine induces GM-CSF, IL-6 and IL-8 in epithelial cells via H1R [32–34] and H4R [35], and promotes eosinophil chemotaxis and adhesion [36]. Epithelial cells play an important role in histamine-mediated inflammation [16].

Increased expression of H1R and H4R was found in AR [16, 34]. To explore the role of H1R and H4R in epithelial

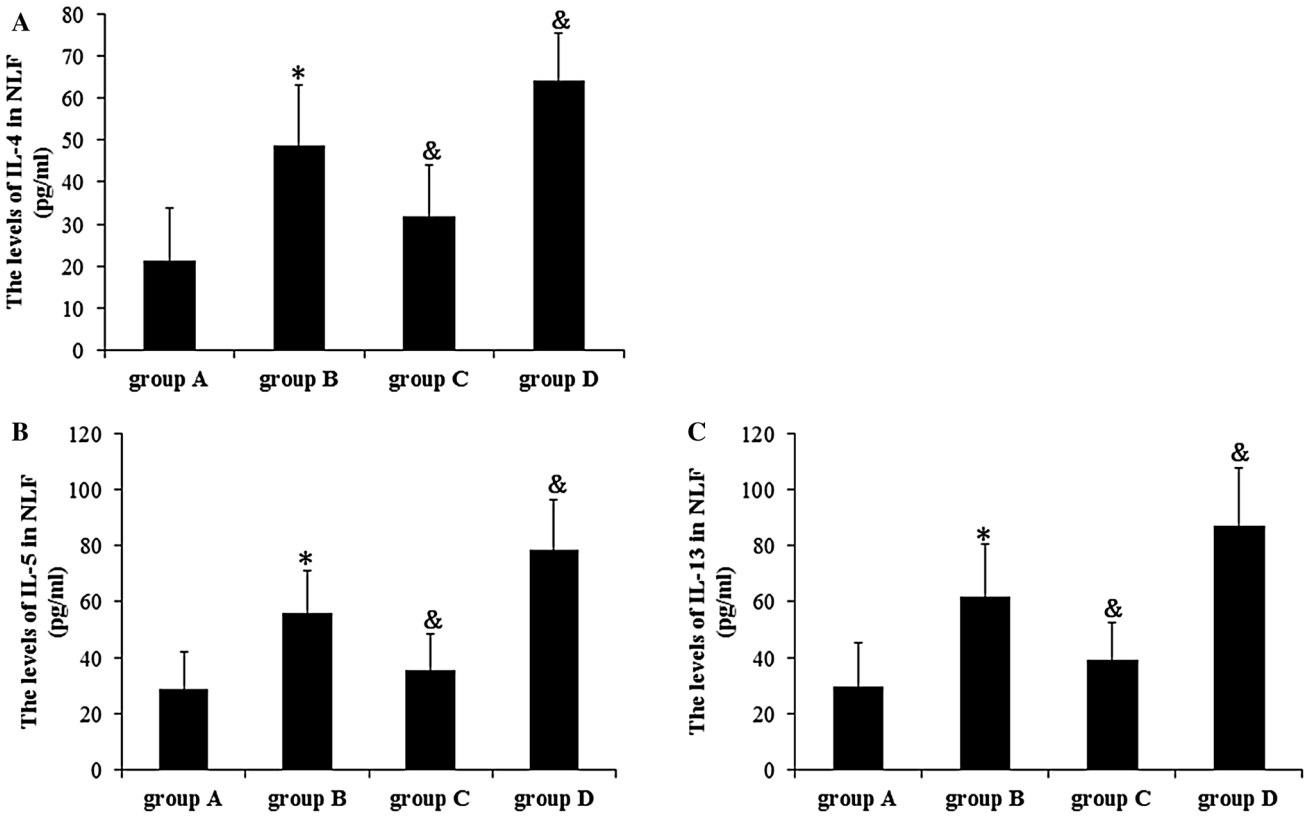

Fig. 5 ELISA assay for IL-14, 5 and 13 in NLF. Group A were immunized with alum before NS challenge and treatment. Group B were immunized with OVA and alum before OVA challenge and NS treatment. Group C were immunized with OVA and alum before OVA challenge and JNJ treatment. Group D were immunized with OVA and alum before OVA challenge and were 4-MH treatment. β-actin was used as loading control. "*" Represents $P < 0.05$ vs group A, and "&" represents $P < 0.05$ vs group B

TSLP production, HNECs were stimulated with histamine in the presence or absence of H1R or H4R agonist. We found that the stimulation with H4R agonist 4-MH prior to histamine significantly up-regulated TSLP expression. Since 4-MH is not a specific receptor for H4R and also bound to H2R [24], we additionally pre-incubated the cells with H4R antagonist JNJ, finding that JNJ pre-incubation decreased TSLP expression induced by 4-MH and histamine. We also showed that H1R agonist showed no effect on TSLP production in this study. These results were consistent with the published evidence that H4R, but not H1R induced TSLP production by keratinocytes and esophageal epithelial cells [24, 31]. Histamine alone tends to enhance TSLP production in our study, while the data were not significant. It was reported that histamine alone did not trigger epithelial TSLP production [24, 31]. The possible reason was that H4R expression was faint in HNECs so that histamine could not induce TSLP production via binding to enough H4R. But histamine significantly increased TSLP expression after 4-MH activated H4R expression in HNECs. Therefore, H4R activation induced epithelial TSLP production, while H1R was not involved in this process.

Although our in vitro results indicated that histamine induced TSLP production by nasal epithelial cells via H4R, it remained unknown whether this effect could be transferred into the in vivo situation of experimental AR. In our study, TSLP expression was up-regulated in the nasal mucosa of sensitized rats, and the treatment with 4-MH further aggravated this change, while JNJ treatment inhibited this effect. Therefore, H4R signaling promoted TSLP production in AR rats. In Th2 polarization, TSLP is found to equip DCs with a programming role [11, 13]. OX40L expression on DCs is directly regulated by TSLP [13], which interacts with OX40 on T cells, leading to Th2 inflammatory response [37]. DCs in the nasal cavity of AR patients were increased [38], and TSLP-mediated DC activation in nasal mucosa initiated Th2 paradigm [39]. Our results indicated that H4R signaling enhanced TSLP-mediated OX40L signaling in the nasal mucosa of AR rats.

Previous studies demonstrated that TSLP-OX40L signaling promoted Th2 inflammatory responses in AR, leading to the increased production of Th2 cytokines [40]. In Th2 immune responses, Th2 cytokines such as IL-4, IL-5 and IL-13 activate immunological effector system assembled

by B cells, eosinophils and mast cells, leading to mast-cell degranulation, IgE production, mucus hypersecretion, and eosinophilic inflammation [13]. The levels of Th2 cytokines are responsible for the allergic immune and inflammatory response in allergic diseases [41]. The levels of IL-4, 5 and 13 in NLF were increased in AR rats in this study, and 4-MH treatment enhanced these effects. But the JNJ treatment inhibited the levels of three cytokines, indicating that H4R promoted Th2-cytokine profile in AR rats. The published report also showed that the deletion of H4R gene or the treatment with H4R antagonists inhibited Th2 responses in asthmatic mice with decreased Th2 cytokines [42]. Recently, group two innate lymphoid cells (ILC2s) are identified to be essential in initiating and driving allergic immune responses [43]. The number of ILC2s was increased in the AR patients, and ILC2s also produced IL-4, 5 and 13 upon activation by epithelial cell-derived cytokines such as IL-33, IL-25 and TSLP [43, 44]. Hence, H4R was very likely to activate ILC2s to enhance Th2-cytokine profile through TSLP.

Although our study supported the role of H4R in Th2-cytokine profile mediated by TSLP and blocking of H4R in AR might be promising to alleviate allergic inflammation via TSLP, H1R is still thought of as an important receptor in AR. Increasing evidence has shown that the combination of H1 and H4 antagonists was more effective than monotherapy with H1R antagonists in allergic diseases, which counteracted the disadvantages of monotherapy [45]. Our current data show that H4R enhances TSLP-OX40L axis in AR, but H4R is also expresses in T cells, and it is not clarified about whether H4R plays a role in OX40 expression on T cells, which is the limitation of this study. Further investigation by us is needed to evaluate whether/how H4R regulates OX40 production on T cells in vitro and in vivo.

Conclusions

H4R activation promoted TSLP production by nasal epithelial cells, leading to the hypersecretion of Th2 cytokines through induction of OX40L expression in the nasal mucosa of AR rats. These factors enhanced Th2 immune responses in AR. Therefore, blocking of H4R in AR might be promising to alleviate allergic inflammation via TSLP.

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Author contributions WWW: Analyzing, acquiring and interpretation the data; YLP: revising the manuscript; HWY: repeating the detection of Th2 cytokines including IL-4 and IL-13 according to the comments of Reviewer #1; BZ: repeating the experiments in mice according to the comments of Reviewer #1; SWS: drafting the article and final approval of the version to be published. We confirm that all the listed authors have participated in the study, and have seen and approved the submitted manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The ethics committee in which all authors worked approved this study. All participants signed the informed consent. The experimental study was approved by the Institutional Review Board of Huzhou University on Principles of Laboratory Animal Care and was performed in accordance with the German Law on Protection of Animals.

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