The expression of adiponectin receptor is altered in mild and moderate/severe persistent allergic nasal mucosa

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ABSTRACT

Background: *Adiponectin, one of the adipokines, has been implicated in the inflammatory process in patients with allergic rhinitis. The level of adiponectin is affected by immunotherapy. Considering the fact that adiponectin receptors (AdipoRs) mediate intracellular signaling events in response to the binding of adiponectin, the role of AdipoRs in healthy and allergic nasal mucosa should be determined. This study investigates the level of expression and distribution pattern of AdipoR1 and AdipoR2 in healthy, mild, and moderate/severe persistent allergic nasal mucosa to understand the role of adiponectin in allergic rhinitis.*

Methods: *The level of expression and distribution pattern of AdipoR1 and AdipoR2 were evaluated in healthy, mild, and moderate/severe persistent allergic nasal mucosa, using semiquantitative reverse-transcriptase–polymerase chain reaction (RT-PCR), immunohistochemistry, and Western blot analysis.*

Results: *AdipoR1 was expressed in healthy, mild, and moderate/severe persistent allergic nasal mucosa where it was commonly localized to the vascular endothelium. However, AdipoR2 was not expressed in any samples of nasal mucosa tested in the present study. Semiquantitative RT-PCR and Western blot analysis showed that the level of expression of AdipoR1 mRNA and protein was decreased in mild and moderate/severe persistent allergic nasal mucosa in comparison with healthy nasal mucosa, but not significantly different between mild and moderate/severe persistent allergic nasal mucosa.*

Conclusion: *These results indicate that AdipoR1 may play an important role in the pathogenesis of allergic nasal mucosa, suggesting a role for AdipoR1 in vascular dysfunction in mild and moderate/severe persistent allergic nasal mucosa.*

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Allergic rhinitis is defined as a chronic nasal inflammatory disease mediated by an IgE-mediated response to environmental allergens and is characterized by recurrent reversible mucosal swelling and nasal hyperreactivity. The mechanism of chronic inflammation in allergic rhinitis is considered dependent on the sustained infiltration and activation of many inflammatory cells, including eosinophils and mast cells, followed by synthesis and release of a variety of proinflammatory mediators and cytokines.[1] Moreover, the diffuse neuroendocrine system such as endocrine-like cells, paracrine-like cells, and peptidergic nerve fibers also play a significant pathophysiological role in allergic rhinitis.[2,3]

Adipose tissue secretes a variety of adipokines, including adiponectin. The identification of adipokines led to the recognition that white adipose tissue represents an important endocrine organ.[4] There is increasing evidence in the literature that adipokines, including adiponectin, play a role in allergic inflammation.[4–6] Adiponectin is considered an anti-inflammatory adipokine because it reduces the production and activity of tumor necrosis factor (TNF) α and interleukin (IL)-6, and the expression of some adhesion molecules, such as intercellular adhesion molecules. Adiponectin also promotes the production of IL-10 and IL-1 receptor antagonist.[4,6] Experimental studies have reported numerous activities exerted by adiponectin on the immune response and showed that adiponectin attenuates allergen-induced airway inflammation and hyperresponsiveness in mice.[4,7]

The activity of adiponectin is mediated by at least two cell membrane receptors (adiponectin receptors 1 and 2 [AdipoR1 and AdipoR2]).[8] Various studies have further indicated that the expression of AdipoRs, as well as adiponectin, is changed in various organs under inflammatory conditions, including asthma, suggesting potential therapeutic targets for the control of various inflammatory diseases.[9,10] Patients with allergic rhinitis have significantly lower serum levels of adiponectin than controls, suggesting the role of adiponectin as a predictor of disease severity in patients with allergic rhinitis.[11] Thus, although adiponectin is relevant to the pathogenesis of allergic rhinitis, precise participation of adiponectin in allergic rhinitis has not been sufficiently evaluated. To elucidate the role of adiponectin in patients with allergic rhinitis, it is necessary to define the expression and distributional pattern of AdipoRs in patient with allergic rhinitis.

In this study, we determined the level of expression and distribution pattern of AdipoR1 and AdipoR2 in healthy nasal mucosa and the nasal mucosa of patients with mild and moderate/severe persistent allergic rhinitis using reverse transcriptase–polymerase chain reaction (RT-PCR), immunohistochemistry and Western blotting analysis.

MATERIALS AND METHODS

Subjects

Thirty patients with mild persistent allergic rhinitis, 29 patients with moderate/severe persistent allergic rhinitis, and 30 healthy control subjects were enrolled in this study. Patients undergoing augmentation rhinoplasty were considered healthy control subjects and were excluded if they had a history of nasal infection or allergy, smoking, or ongoing drug treatment. All patients with allergic rhinitis had typical symptoms of perennial nasal allergy, nasal eosinophilia, and a positive skin test or positive radioallergosorbent test to house-dust mites, as well as positive reactions on provocation tests. Nasal provocation test was performed using solutions containing extracts of Dp and Df (both: 5000 BU/mL; Allergopharma, Reinbeck, Germany). Serum total IgE (IU/mL) was determined by enzyme-linked immu-

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nosorbent assay method (CAP system). The detectable range of the assay for total IgE is 2–2000 IU/mL. Allergic patients with exacerbation of upper respiratory infection during the 6 weeks preceding the study were not included. Other exclusion criteria included current smoking; a medical history of recurrent infections of the respiratory tract; and use of topical or oral corticosteroids, leukotriene modifiers, and antihistamines during the 8 weeks that preceded the study.

Thirty pieces of healthy nasal mucosa were obtained from the inferior turbinate of 30 healthy control subjects (22 men and 8 women; age range, 20–44 years) who had normal nasal mucosa and were admitted for augmentation rhinoplasty. A mucosal biopsy sample was obtained ~2 cm posterior to the anterior edge of the inferior turbinate using Blakesley forceps with a cup diameter of 4 × 10 mm.

Fifty-nine patients with persistent allergic rhinitis were classified by disease severity according to the Allergic Rhinitis and Its Impact on Asthma guideline as mild or moderate/severe.[12] Patients with moderate/severe rhinitis had one or more of the following symptoms: sleep disturbance, impairment of daily activities, leisure and/or sports, and impairment of school or work, or troublesome symptoms. Patients with mild rhinitis had none of these symptoms.

Sample Preparation

Nasal biopsy specimens were also obtained from the inferior turbinate of all patients with mild (22 men and 8 women; age range, 24–47 years) and moderate/severe persistent allergic rhinitis (20 men and 9 women; age range, 22–45 years) using a Blakesley forceps with a cup diameter of 4 × 10 mm under local anesthesia. A mucosal biopsy sample was obtained ~2 cm posterior to the anterior edge of the inferior turbinate. As control tissue, subcutaneous adipose tissues were obtained from the abdomen of patients with frontal sinusitis during frontal sinus obliteration procedure. Before obtaining the tissue specimens, the protocols and informed consent form were approved by the Institutional Review Boards for human beings at our institution, and all participants gave written informed consent.

All tissue samples were divided into three portions. The first and second portions were frozen in liquid nitrogen and stored at −70°C for protein and total RNA isolation. For immunohistochemistry, the third portion was immersed overnight in a freshly prepared fixative containing 4% paraformaldehyde in phosphate-buffered saline (PBS; pH 7.4). All samples were then dehydrated in a graded series of ethanol to xylene and embedded in paraffin wax.

Total RNA Isolation, RT-PCR, and Semiquantitative RT-PCR

Total RNA (1 μg) from each sample was reverse transcribed in 20 μL of a reaction mixture containing 2.5 U of Moloney murine leukemia virus RT (GIBCO BRL, Grand Island, NY) and 50 pmol of random hexanucleotides at 42°C for 60 minutes. RNA integrity and the success of the reverse transcription reaction were monitored by PCR amplification of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) transcripts. Negative controls consisted of omission of the RT enzyme from the cDNA synthesis for each specimen. The primer sequences of each gene used in the study are listed in Table 1.

Semiquantitative RT-PCR was performed on the samples to assess the differential expression of each gene mRNA in healthy and allergic nasal mucosa. The optimum number of PCR cycles for each cDNA species was determined by plotting the PCR product yield of different cycles on a semilogarithmic graph and the cycle number representing exponential amplification was chosen for the final amplification. For quantification of the PCR products of all samples, the expected bands were analyzed by densitometry and the data were expressed as the ratio of each gene to the corresponding GAPDH cDNA.

Immunohistochemical and Western Blot Analysis

Immunohistochemical staining was performed using a peroxidase-labeled streptavidin-biotin technique. Briefly, paraffin sections (4 μm) were cut and placed on poly-L-lysine–coated glass slides. Sections were treated with 0.03% H_2O_2 in methanol for 15 minutes to quench endogenous peroxidase activity. After washing in PBS, the sections were incubated overnight at 4°C with a 1:100 dilution of anti-AdipoR1 or a 1:100 dilution of anti-AdipoR2 antibody (Santa Cruz Biotechnology, Inc., Santa Cruz, CA). The color was developed using 3,3′-diaminobenzidine. To assess the staining intensity, independent examination by two different investigators was used in all tissue sections. The intensity was classified into four degrees as follows: −, negative; +, weakly positive; ++, moderately positive; and +++, strongly positive. Quantitative analyses of this intensity for each patient were calculated as the mean of the total score in the tissue specimen. As a negative control, the primary antibodies were replaced with nonimmune goat IgG (Santa Cruz Biotechnology, Inc.).

For Western blot analysis, frozen tissue was crushed and vigorously vortexed in a buffer solution containing 50 mM of Tris-HCl (pH 8.0), 150 mM of NaCl, and a proteinase inhibitor cocktail. Extracted protein (50 μg) was resuspended in sodium dodecyl sulfate sample buffer and boiled for 5 minutes. Equal amounts of total protein were separated on 12% sodium dodecyl sulfate–polyacrylamide gels and transferred to immobilon (Millipore, Bedford, MA). The blots were blocked for 1 hour at room temperature with PBS-T containing 1% skim milk and then incubated with anti-AdipoR1 and anti-AdipoR2 antibody in PBS-T overnight at room temperature. Antibody reactions were detected using the enhanced chemiluminescence detection kit (GE Amersham Bioscience, Buckinghamshire, U.K.), followed by detection of chemiluminescence on x-ray film. As an internal control, β-actin expression was analyzed in parallel blots using the β-actin antibody (Sigma, St. Louis, MO). The intensity of detected bands was quantified using scion image Beta 4.0.2 (Scion Corp., Frederick, MD). The relative intensities of each protein signal were obtained by dividing the intensity of each protein signal by the β-actin signals.

Table 1 **Sequences of polymerase chain reaction primers specific for AdipoR1 and AdipoR2**

Primer	Size (bp)	Sequence
AdipoR1	375	S: 5′-CCTTTCCCCAAGCTGAAGCTGC-3′ AS: 5′-CCTTGACAAAGCCCTCAGCGAT-3′
AdipoR2	311	S: 5′-ATAGGGCAGATAGGCTGGTTGA-3′ AS: 5′-GGATCCGGGCAGCATACA-3′
GAPDH	502	S: 5′-ATCTTCCAGGAGCGA GATCC3′ AS: 5′-ACCACTGACACGTTGGCAGT-3′

Annealing temperature = 57°C.
AdipoR1 = adiponectin receptor 1; AdipoR2 = adiponectin receptor 2; GAPDH = glyceraldehydes-3-phosphate dehydrogenase.

Statistical Analysis

Statistical analyses were performed using the SPSS for Windows software package Version 16.0.0 (SPSS, Inc., Chicago, IL). The age and body mass index (BMI) differences in the three groups were calculated by one-way ANOVA, and the Bonferroni *post hoc* correction was applied. The duration of rhinitis between the mild and moderate/severe persistent rhinitis groups was statistically evaluated by the Mann-Whitney *U* test. Kruskal-Wallis test was performed to establish statistically significant differences in values obtained from the nasal mucosa of healthy controls and the patients with mild and moderate/severe persistent allergic rhinitis. The level of significance was set at $p < 0.05$. Mann-Whitney's *post hoc* tests were performed to compare differences between different groups.

RESULTS

The characteristics of healthy controls and patients with mild or moderate/severe persistent allergic rhinitis are shown in Table 2. The

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Table 2 **Clinical characteristics of patients**

Characteristics	Healthy Nasal Mucosa (n = 30)	Mild Persistent Allergic Rhinitis (n = 30)	Moderate/Severe Persistent Allergic Rhinitis (n = 29)
Sex (female %)	27%	27%	31%
BMI (kg/m^2)	23.09 ± 0.56	24.07 ± 0.45	23.57 ± 0.89
Age (yr)	33.7 ± 6.2	35.4 ± 7.9	33.9 ± 7.8
Rhinitis duration (yr)	NA	11.78 ± 1.3	12.43 ± 1.73
Serum total IgE (IU/mL)	100.34 ± 98.20	505.23 ± 202.85	528.04 ± 250.76
Nasal eosinophils	0–1/2+	1–4+	1–4+

BMI = body mass index.

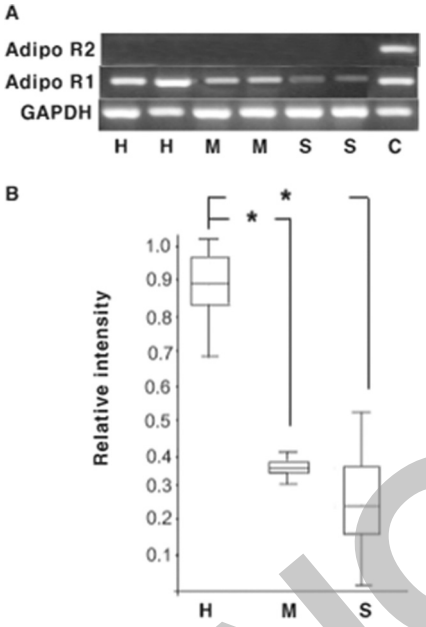

Figure 1. *(A) Semiquantitative reverse transcriptase—polymerase chain reaction (RT-PCR) analysis of adiponectin receptor 1 (AdipoR1) and AdipoR2 mRNA level in healthy (H; n = 30), mild (M; n = 30), and moderate/severe (S; n = 29) persistent allergic nasal mucosa, and control tissue (C). (B) Bands were quantified by densitometric scanning and the relative amount of each gene was calculated by dividing by the internal control, glyceraldehyde-3-phosphate dehydrogenase (GAPDH). The bottom and top of the box are the lower and upper quartiles, respectively, and the band near the middle of the box is the median. *p < 0.05.*

three groups were comparable with respect to BMI, age, and gender distribution (Table 2). The duration of rhinitis was not significantly different between patients with mild and moderate/severe persistent allergic rhinitis (Table 2). However, the serum total IgE levels were increased in patients with mild and moderate/severe persistent allergic rhinitis compared with healthy controls (Table 2).

The expression of AdipoR1, AdipoR2, and GAPDH mRNA was determined by RT-PCR in total RNA preparations isolated from healthy and allergic nasal mucosa. The PCR products of the expected size were 375 bp for AdipoR1, 311 bp for AdipoR2, and 502 bp for GAPDH. As shown in Fig. 1, AdipoR1 was expressed in healthy, mild, and moderate/severe persistent allergic nasal mucosa and showed 100% sequence homology with the published sequence. However, AdipoR2 was not expressed in any samples of healthy and allergic nasal mucosa tested. Nevertheless, both receptors were expressed in the adipose tissues used as control tissues (Fig. 1 *A*). Negative control reactions without RT in the cDNA synthesis process showed no bands, indicating that there was no contamination by genomic DNA in the RNA samples (data not shown). The relative intensity of AdipoR1 with respect to GAPDH was significantly decreased in mild and moderate/severe persistent allergic nasal mucosa compared with healthy nasal mucosa (Fig. 1 *B*). However, the relative intensity is not significantly different between mild and moderate/severe persistent allergic nasal mucosa (Fig. 1 *B*).

Immunohistochemical staining showed a homologous pattern in all samples of nasal mucosa from healthy and allergic turbinate mucosa (Fig. 2). In healthy, mild, and moderate/severe persistent allergic nasal mucosa, AdipoR1 was commonly localized to the vascular endothelium. However, the staining intensity of AdipoR1 was greater in healthy nasal mucosa and decreased in mild and moderate/severe persistent allergic nasal mucosa (Fig. 2; Table 3). AdipoR2 was not expressed in any samples tested in the present study (not shown). The nonimmune isotype control did not show any staining (not shown).

Western blot analysis with the AdipoR1 antisera detected proteins in healthy, mild, and moderate/severe persistent allergic turbinate mucosa (Fig 3) whereas the band for AdipoR2 antisera was not detected in any samples. However, both receptors were found in adipose tissue used as control tissues (Fig. 3). The relative abundance of AdipoR1 with respect to β-actin was significantly decreased in mild and moderate/severe persistent allergic nasal mucosa compared with healthy turbinate mucosa, showing that the levels of expression of AdipoR1 was decreased in mild and moderate/severe persistent allergic nasal mucosa compared with healthy nasal mucosa. The level of expression of AdipoR1 was not significantly different between mild and moderate/severe persistent allergic nasal mucosa (Fig. 3).

DISCUSSION

To achieve a more comprehensive view of AdipoR1 and AdipoR2 in healthy human and allergic nasal mucosa, we evaluated the level of expression and the pattern of distribution of AdipoR1 and AdipoR2 in healthy and allergic human nasal mucosa. At the mRNA level, AdipoR1 was expressed in healthy and allergic human nasal mucosa. The immunohistochemical examination revealed that AdipoR1 is exclusively localized to the vascular endothelium in all patients and the staining intensity of AdipoR1 is higher in healthy nasal mucosa compared with mild and moderate/severe persistent allergic nasal mucosa. These immunohistochemical results were verified with Western blot analysis. Taken together, our data indicate that AdipoR1 is expressed in healthy human nasal mucosa and is down-regulated in mild and moderate/severe persistent allergic nasal mucosa, suggesting that AdipoR1 may play an important role in the pathophysiology of allergic rhinitis. This is the first detailed analysis regarding the expression and pattern of distribution of AdipoR1 mRNA and protein in healthy, mild, and moderate/severe persistent allergic nasal mucosa.

There is evidence that obesity and weight gain are linked with allergic diseases, probably through the immunologic effects of adipose tissue. It is known that the association between obesity and respiratory allergy may, at least in part, depend on decreased immunologic tolerance to the allergen as a consequence of immunologic changes induced by adipokines, including adiponectin, and some

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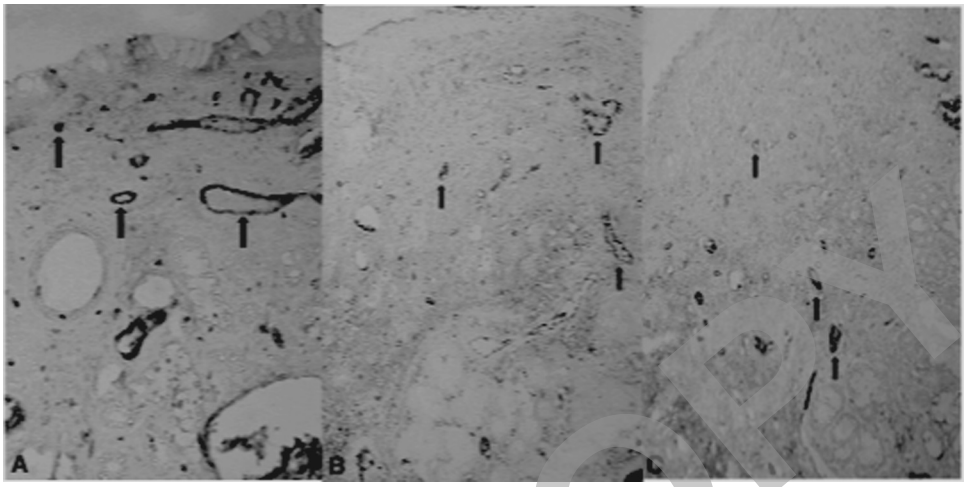

Figure 2. Immunohistochemical localization of adiponectin receptor 1 (AdipoR1) in (A) healthy, (B) mild, and (C) moderate/severe persistent allergic nasal mucosa. Arrow indicates vascular endothelium (original magnification, ×100).

Table 3 **Distribution pattern of AdipoR1 in healthy, mild, and moderate/severe persistent allergic nasal mucosa**

	Healthy Nasal Mucosa	Allergic Nasal Mucosa	
		Mild Persistent	Moderate/Severe Persistent
Endothelium	+++	+	+

AdipoR1 = adiponectin receptor 1.

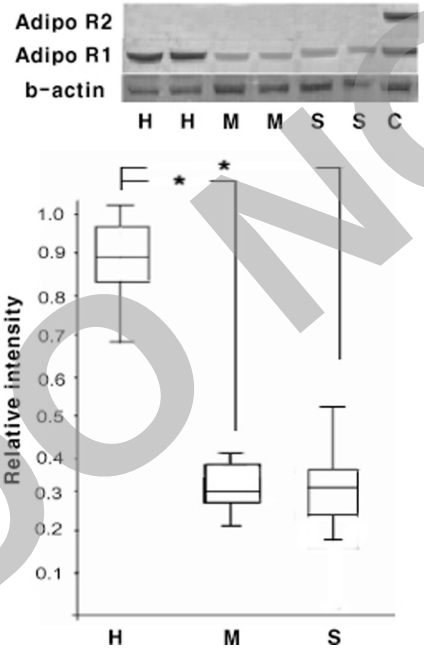

*Figure 3. (A) Western blot analysis of adiponectin receptor 1 (AdipoR1) and AdipoR2 in healthy (H; n = 30), mild (M; n = 30), and moderate/severe (S; n = 29) allergic nasal mucosa, and control tissue (C). (B) Bands were quantified by densitometric scanning and the relative amount of each gene was calculated by dividing by the internal control (β-actin). The bottom and top of the box are the lower and upper quartiles, respectively, and the band near the middle of the box is the median. *p ≤ 0.05.*

proinflammatory cytokines, including IL-6 and TNF-α, secreted by white adipose tissue.[13] Most studies have reported associations between obesity and asthma but there is less consistency about the relationship with allergic rhinitis and conjunctivitis.[14,15] Nevertheless, recently published clinical studies provided evidence that adiponectin may play a role in allergic rhinitis, but the results were inconsistent.[11,16] Hsueh *et al.*[11] showed that patients with allergic rhinitis had lower adiponectin levels compared with controls, suggesting that adiponectin levels may serve as predictors of disease severity in childhood allergic rhinitis. Ciprandi *et al.*[16] reported that adiponectin levels were significantly higher in patients with allergic rhinitis than in control groups. It has been shown that immunotherapy may affect the level of expression of adiponectin in patients with seasonal allergic rhinitis, suggesting a role for adiponectin in patients with allergic rhinitis.[17] Therefore, the exact molecular mechanisms that alter the level of expression of adiponectin in patients with allergic rhinitis are not fully known. Proinflammatory cytokines, such as IL-1ß and IL-6, have been reported to inhibit the expression of adiponectin in adipocytes.[4] However, a study that determined the serum levels of adiponectin in patients with allergic rhinitis did not find a significant correlation between proinflammatory cytokines and adiponectin.[11] Therefore, additional studies to determine the exact role of adiponectin in allergic rhinitis are needed.

Considering that AdipoRs mediate intracellular signaling events in response to binding adiponectin, including increased adenosine 5′-monophosphate kinase and peroxisome-activator receptor-α ligand activity, we determined the level of expression and distribution pattern of AdipoR1 and AdipoR2 to understand the possible role of adiponectin in patients with allergic rhinitis. In humans, both AdipoR1 and AdipoR2 are highly expressed in many tissues and organs including the liver, adipose tissue, and pancreas.[18,19] Generally, the level of expression of AdipoR2 is weaker and more restricted than AdipoR1 in most tissues.[18,19] The expression of AdipoR1 and AdipoR2 is reportedly regulated under various physiological and pathophysiological states.[20] The expression of both receptors is lower in periodontal tissues from patients with severe periodontitis than in patients with healthy periodontal tissues, suggesting that adiponectin may not function efficiently in sites of periodontal disease because of a decrease in the number of receptors.[20] A study assessing the expression of AdipoR2 in placenta showed that the change in the level of expression of AdipoR2 was more evident in patients with severe preeclampsia, indicating that the expression of AdipoR2 was consistent with the severity of preeclampsia.[21] Using an allergic asthma model, Shore *et al.*[7] showed that ovalbuman challenge decreased mRNA expression of AdipoR1 and AdipoR2 and suggested that allergen challenge might reduce the beneficial effects of adiponectin on the lungs by attenuating proposed components of adiponectin-signaling pathways.[7] The present study also showed that AdipoR1 is expressed in healthy, mild, and moderate/severe persistent allergic nasal mucosa, but AdipoR2 was not expressed in any of the three groups

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tested in the present study. The present results are in accordance with the results showing that immunohistochemical studies of lung section from subjects with chronic obstructive pulmonary disease showed that airway epithelial cells expressed significant levels of AdipoR1 but not AdipoR2.[9] Moreover, in our study, the level of expression of AdipoR1 mRNA and protein in mild and moderate/severe persistent allergic nasal mucosa was decreased in comparison with healthy nasal mucosa. Considering these results, decreased level of expression of AdipoR1 in patients with allergic rhinitis may aggravate the symptoms of allergic rhinitis by reducing the effects of adiponectin on nasal mucosa. This suggestion is supported by the experimental results that adiponectin attenuates allergen-induced airway inflammation.[7] In addition, gender differences in the level of expression of adiponectin in allergic rhinitis have been shown previously, although the results are not consistent.[16,17] In the present study the three groups were comparable with respect to BMI, age, and gender distribution, indicating that there might not be BMI, age, and gender difference in the level of expression of AdipoR1 in patients with mild and moderate/severe allergic rhinitis.

To investigate the possible function of adiponectin in allergic rhinitis in more in detail, the localization of both receptors, AdipoR1 and AdipoR2, needs to be evaluated in healthy and allergic nasal mucosa. Here, we showed that AdipoR1, but not AdipoR2, is exclusively expressed in the endothelium of healthy and allergic nasal mucosa. In allergic nasal mucosa, irrespective of mild or moderate/severe persistent allergic rhinitis, the staining intensity of AdipoR1 was decreased in comparison with healthy nasal mucosa. These results raise the possibility that adiponectin may induce the endothelial dysfunction in mild and moderate/severe persistent allergic rhinitis. Unfortunately, the current study did not find the difference in the level of expression of AdipoR1 between mild and moderate/severe persistent allergic rhinitis. It is possible that frequency and duration of symptoms, rather than severity, may alter levels of AdipoR1 in patients in allergic rhinitis. This suggestion is supported by a study showing moderate/severe persistent allergic rhinitis is characterized by a significantly greater eosinophilic and predominantly Th2 cell–mediated nasal inflammatory profile compared with intermittent allergic rhinitis.[22] However, our study did not evaluate patients with intermittent allergic rhinitis, and future studies looking at AdipoR1 expression in this phenotype may be promising. Previous studies have repeatedly documented a close association between adiponectin deficiency and the development of almost every stage of vascular disease and reported that adiponectin exerts multiple vasculoprotective effects through anti-inflammatory actions on endothelial cells such as antioxidant activities in the endothelium, suppression of the leukocyte–endothelium interactions, and decreased expression of adhesion molecules.[23] Collectively, these data suggest that the deficiency of AdipoR1 may contribute to the pathogenesis of mild and moderate/severe persistent allergic rhinitis through derangement of the aforementioned activities.

CONCLUSION

Our study showed that AdipoR1 is expressed in healthy and allergic nasal mucosa where AdipoR1 is specifically localized to the vascular endothelium. The level of AdipoR1 was down-regulated in mild and moderate/severe persistent allergic nasal mucosa compared with normal nasal mucosa. Based on these results and the published literature, altered level of expression of adiponectin and its receptor AdipoR1 in allergic nasal mucosa may play an important role in the pathogenesis of allergic rhinitis through vascular dysfunction.

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