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Local Effect of Neurotrophin-3 in Neuronal Inflammation of Allergic Rhinitis: Preliminary Report

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Background: Allergic rhinitis is a common inflammatory nasal mucosal disease characterized by sneezing, watery nasal discharge, nasal obstruction and itching. Although allergen-specific antibodies play a main role in the allergic airway inflammation, neuronal inflammation may also contribute to the symptoms of allergic rhinitis. Neuronal inflammation is primarily caused by the stimulation of sensory nerve endings with histamine. It has been shown that neurotrophins may also have a role in allergic reactions and neuronal inflammation. Nerve growth factor, neurotrophin 3 (NT-3), neurotrophin 4/5 and brain-derived neurotrophic factor are members of the neurotrophin family. Although nerve growth factor and brain-derived neurotrophic factor are well studied in allergic rhinitis patients, the exact role of Neurotrophin-3 is not known.

Aims: To investigate the possible roles of neurotrophin-3 in allergic rhinitis patients.

Study Design: Case-control study.

Methods: Neurotrophin-3 levels were studied in the inferior turbinate and serum samples of 20 allergic rhinitis and 13 control patients. Neurotrophin-3 staining of nasal tissues was evaluated by immunohistochemistry and ELISA was used for the determination of serum Neurotrophin-3 levels.

Results: Neurotrophin-3 staining scores were statistically higher in the study group than in the control patients (p=0.001). Regarding serum Neurotrophin-3 levels, no statistically significant difference could be determined between allergic rhinitis and control patients (p=0.156). When comparing the serum NT-3 levels with tissue staining scores, there were no statistically significant differences in the allergic rhinitis and control groups (p=0.254 for allergic rhinitis and p=0.624 for control groups).

Conclusion: We suggest that Neurotrophin-3 might affect the nasal mucosa locally without being released into the systemic circulation in allergic rhinitis patients.

Keywords: Airway, allergic rhinitis, inflammation, neuronal, neurotrophin-3, rhinitis

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Allergic rhinitis (AR) is an IgE-mediated inflammatory disorder induced after exposure to environmental allergens. Characteristic symptoms include rhinorrhea, nasal itching, sneezing, and nasal congestion (1). Also, allergic airway inflammation and hyper-responsiveness to nonspecific stimuli is controlled by neuronal mechanisms in AR patients (2). One of the alternative pathways in the pathogenesis of AR is neuronal inflammation caused by the stimulation of sensory nerve endings with histamine. Histamine also causes the release of neurotransmitters such as neurokinin A (NKA), Substance P (SP) and calcitonin gene related peptide (CGRP) (3). SP has effects on mast cell degranulation, increased vascular permeability, mucus secretion, leukocyte chemotaxis, fibroblast proliferation, and cytokine (IL-1β, 2, 3, 4, 5 and 6 and TNF-α) synthesis, which contribute to the symptoms of AR (4,5). Recently, new molecules and histamine receptors have been found for AR pathogenesis. Histamine 4 receptor (H4R) is a new histamine receptor which is expressed by hematopoietic cells such as dendritic cells, T cells, mast cells, and peripheral leukocytes. It has been shown to be effective in the cascade of allergic reactions and H4R receptors may have a role in allergic diseases (6). It has also been shown that neurotrophins may play a role in allergic and neuronal inflammation (7-11).

Neurotrophins are a group of nerve growth factors which are primarily responsible for the growth and differentiation of nervous tissues. Nerve growth factor (NGF), Neurotrophin-3 (NT-3), neurotrophin 4/5 and brain-derived neurotrophic factor (BDNF) are members of the neurotrophin family [5]. NGF specifically binds to its receptor Tropomyosin receptor kinase (Trk) A, BDNF and NT 4/5 bind to the Trk B receptor and NT-3 specifically binds to the Trk C receptor (8). It has been suggested that they may play a role in the pathogenesis of allergic reactions because of the high serum levels of NGF and BDNF in patients with allergic diseases (12,13). Some neurotrophins like BDNF and NGF are studied in AR and their potential effects are shown, but the probable role of NT-3 in AR is not actually known (3,14). In this study, we aimed to investigate the possible role of NT-3 in allergic rhinitis patients using serum levels and immunohistochemical examination of NT-3 in nasal mucosal tissue.

MATERIALS AND METHODS

Local ethical committee approval was acquired for our study. Written informed consent from patients was obtained in both the AR and control groups. Power analysis of the study was performed as outlined by previous published articles concerning the relationship between neurotrophins and allergic rhinitis. The result of the power analysis was 6 for each group. We included 20 patients with AR and 13 control group patients with concha bullosa.

There were eight (40%) male and twelve (60%) female patients in the AR group. The age of AR patients was between 21 and 41 and the mean age was 30.3 years. In the control group, there were eleven (84.6%) males and two (15.4%) females. The age of control group was between 18 and 40, with a mean age of 28 years. There was a slight difference (p=0.011) between groups regarding sex, whereas there was no statistically significant difference between groups regarding the age of patients (p=0.306).

Nasal endoscopy was performed for all patients and the control group using 0° and 30° rigid telescopes. The skin prick test was performed for all AR group patients. Total and specific blood IgE levels (N-Latex Mono, Germany) were also measured for the diagnosis of AR. Sixteen allergens including positive and negative controls were used in the skin prick test (Stallergenes®, France). Control group patients were selected from individuals who had been operated on for concha bullosa of the middle turbinate without rhinitis symptoms using paranasal sinus computerized tomography and nasal endoscopic examination findings. Patients with systemic diseases including rheumatoid arthritis, diabetes mellitus, hypo/hyperthyroidism, hypertension, and neurological diseases such as Parkinsonism, chorea, etc. were excluded from the study as control group patients. Inclusion and exclusion criteria for the study group patients are shown in Table 1.

TABLE 1. Study group patient selection criteria

Inclusion criteria for study
Age between 16-45 years
Positive skin prick test or
Positive result of at least one of the serum specific IgE values
Symptoms for more than one year
No infection signs on nasal endoscopy
Exclusion criteria for study
Previous systemic corticosteroid usage at most one month before
Previous nasal corticosteroid usage at most one month before
Previous nasal sodium cromoglicate or neodocromyl sodium usage at most one month before
Previous nasal or systemic antihistaminic usage at most one month before
Infection signs on nasal endoscopy
Pregnancy or lactation
Nasal polyp
Systemic diseases including rheumatoid arthritis, diabetes mellitus, hypo/hyperthyroidism, hypertension, neurological diseases such as Parkinsonism, chorea, etc.

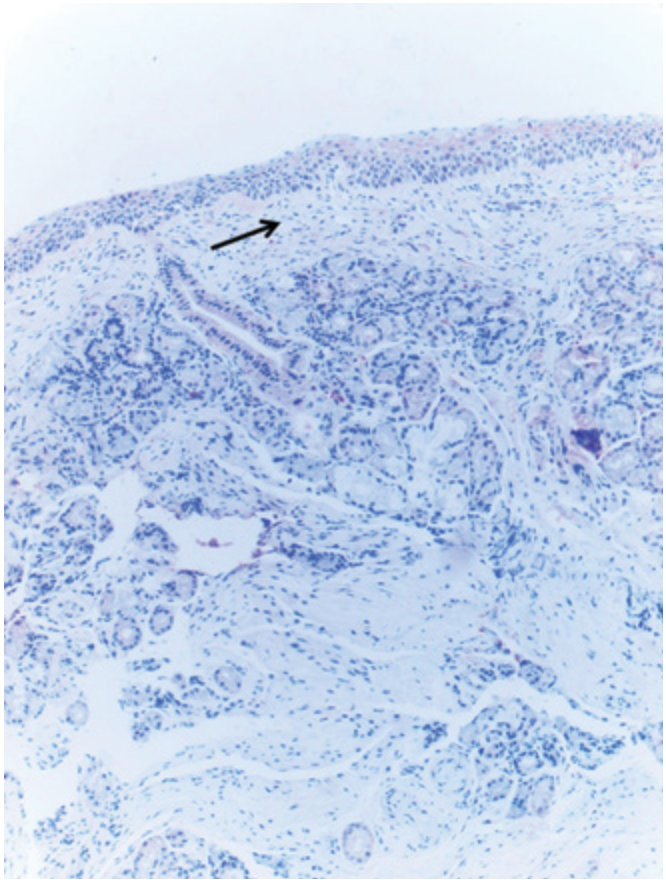

FIG. 1. Very rare (+1) staining of NT-3 in the nasal mucosa (black arrow shows NT-3 staining in interstitial matrix)

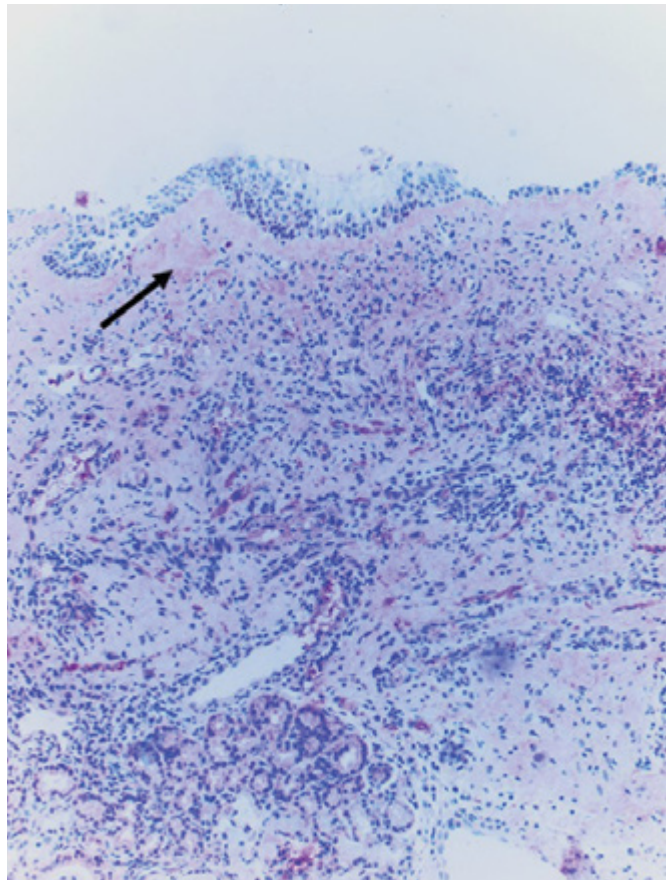

FIG. 2. Very severe (+5) staining of NT-3 in the nasal mucosa (black arrow shows NT-3 staining in interstitial matrix)

Inferior turbinate biopsies for NT-3 staining levels

After providing information about the biopsy procedure to the AR patients, 10% lidocaine spray was administered to the inferior turbinates. Mucosal samples were taken from the inferior turbinate using microcup forceps. For the control group, the concha bullosa mucosa was excised during surgery under general anesthesia. The biopsy specimens and concha bullosa mucosa were fixed in 10% formalin solution. Five μm sections were obtained from formalin-fixed, paraffin-embedded tissues of all biopsies and routine H&E staining was performed. The sections were immunostained for NT-3 (Santa Cruz, Texas, USA, dilution 1:200) according to the instructions of the manufacturer, as described by Arellano et al. (15). For the negative control, specimens were processed in the absence of a primary antibody. The staining of NT-3 was observed in interstitial matrix. Briefly, the intensity of immunostaining was analyzed. The staining intensity was scored semi-quantitatively in five groups: very rare (+1), mild (+2), moderate (+3), severe (+4) and very severe (+5); this was following microscopic examination as outlined by Raap et al. (16). In contrast to their method, the mildest staining score was +1, since all of our tissue biopsies showed more or less staining with NT-3. The pathologist was blinded to the group of tissue samples during immunohistochemical analysis. Very rare and very severe staining levels in the tissue specimens are shown in Figures 1 and 2, respectively.

Measurement of serum NT-3 levels

Venous blood samples were collected from patients for the measurement of serum levels of NT-3 by using an enzyme-linked immunosorbent assay (ELISA). Serum NT-3 level was measured using a sandwich-ELISA kit (ChemiKine, USA) with the instructions described by Zhang et al. (17). The results were assessed as pg/mL.

Statistical analysis

Statistical analysis was performed using SPSS version 16.0 (SPSS Inc. Chicago/USA-2007). The Mann-Whitney U test was used to compare the serum NT-3 levels of the two groups because the AR group did not have a normal distribution. The Mann-Whitney U test was also used for the comparison of nasal tissue NT-3 staining levels as a nonparametric test.

TABLE 2. NT-3 staining scores of nasal tissue biopsies and serum NT-3 levels (pg/mL) of AR and control groups

Patient Number	AR group nasal tissue staining scores (n=20)	Control group nasal tissue staining scores (n=13)	AR serum NT-3 levels (n=20)	Control group serum NT-3 levels (n=13)
1	+3	+2	54.07	127.7
2	+3	+2	491.9	120.6
3	+5	+3	7.678	237.2
4	+3	+1	10.27	107.5
5	+3	+2	27.59	135.8
6	+5	+2	137.1	137.8
7	+3	+2	445.2	321.4
8	+4	+1	498.3	141.1
9	+3	+1	15.22	348.4
10	+3	+1	66.25	52.38
11	+5	+2	224.5	95.63
12	+1	+2	57.44	351.6
13	+1	+2	6.738	93.75
14	+1		13.98	
15	+3		93.75	
16	+3		257.9	
17	+3		9.037	
18	+2		111.3	
19	+3		178.8	
20	+3		153.2	
p values	0.001		0.156	

AR: allergic rhinitis; NT-3: neurotrophin 3

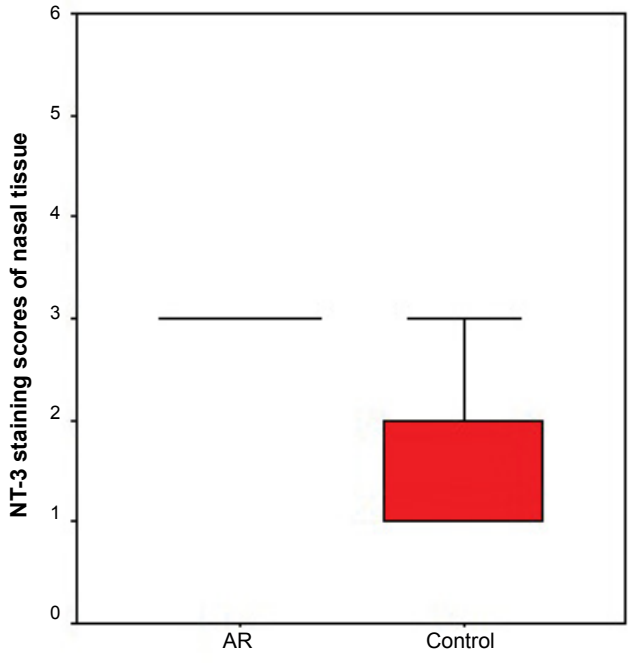

FIG. 3. Median values of tissue NT-3 staining levels of AR patients and control group (NT-3: neurotrophin 3; AR: allergic rhinitis)

Correlation coefficient was used for comparing serum levels with tissue staining scores.

RESULTS

NT-3 staining levels of nasal tissue biopsy specimens of AR patients were higher than in the control group (p=0.001). Median values of nasal tissue NT-3 staining of AR and control groups were +3 and +2, respectively, as shown in Figure 3.

When serum NT-3 levels of AR patients and the control group were compared, there was no statistically significant difference between the two groups (p=0.156). Serum NT-3 levels and NT-3 staining scores of the AR and control groups are given in Table 2. Median values of the AR and control group serum NT-3 levels are given in Figure 4.

Regarding a comparison of nasal mucosa staining scores with serum NT-3 levels, there were no statistically significant differences in the AR and control groups (p=0.254 for AR and p=0.624 for the control group).

TABLE 3. Studies concerning the role of neurotrophins in Allergic Rhinitis

Author	Published year	Studied Neurotrophin type (s) and methods	Result
Sanico et al. (22)	2000	NGF (Nasal lavage fluid with protein electrophoresis and ELISA before and after nasal provocation)	NGF expression in nasal fluid is increased in AR and there is a dose dependent increase after nasal provocation
Raap et al. (16)	2008	NGF, BDNF (serum with ELISA and tissue biopsy with immunohistochemistry before and after nasal provocation)	NGF and BDNF expression increases in nasal tissue after nasal provocation, but increment in serum levels is not statistically significant.
Raap et al. (23)	2008	NGF, BDNF, NT-3 (peripheral blood cytofluorometry and chemotaxis for analysis of neurotrophin receptors Trk A, B, C.)	Neurotrophin receptors Trk A, B and C are up-regulated in AR
Gelincik et al. (2)	2012	NGF (tissue biopsy with immunofluorescence and immunohistochemistry)	NGF expression increases in both AR and idiopathic rhinitis in the nasal tissue
Ismi et al.*	Presented study	NT-3 (Nasal tissue biopsy with immunohistochemistry and serum with ELISA)	NT-3 staining levels in nasal tissue are higher in AR group, but serum levels are not statistically significant

*Presented study
NGF: nerve growth factor; BDNF: brain-derived neurotrophic factor; NT-3: neurotrophin 3; ELISA: enzyme-linked immunosorbent assay; Trk: tropomyosin receptor kinase; AR: allergic rhinitis

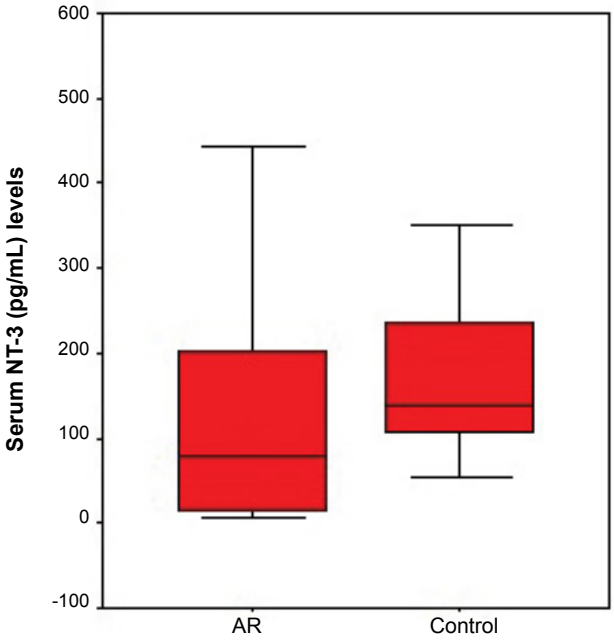

FIG. 4. Median serum NT-3 levels of AR and control groups (NT-3: neurotrophin 3, AR: allergic rhinitis)

DISCUSSION

Allergic rhinitis (AR) is the most common atopic disease, the pathology and symptoms of which are well known. AR occurs in a type 1 hypersensitivity reaction in which the cardinal symptoms of rhinitis (sneezing, watery nasal discharge, nasal obstruction and itching) are initiated by mast cell degranulation and histamine release (18,19). In addition to these well-known pathways, alternative pathways are also responsible for the pathogenesis of AR.

Neurotrophins are proteins which have similar receptor affinities and biological effects. The prototype of the neurotrophin family is NGF. BDNF, NT-3 and NT-4/5 are the other members (7). Although neurotrophins show their effects primarily on the nervous system after binding to their receptors, they have also some effects in allergic inflammation (7-11). Increasing levels of neurotrophins in bronchoalveolar lavage fluid after allergen exposure in allergic asthmatic patients was shown. The source of neurotrophins in allergic asthmatic patients are airway epithelium, alveolar and interstitial macrophages and smooth muscle cells (7,20). Neurotrophins contribute to allergic inflammation by increasing Th-2 activity. In rat models, neurotrophin Trk-C receptors are found in Th-2 lymphocytes, but not in Th-1 (7). It has also been shown that neurotrophins can contribute to inflammatory mediator secretion in allergic diseases (20). Neurotrophin mRNA levels were studied on blood eosinophils in allergic asthmatic patients and mRNA levels were higher in the allergic group than in the control group (21). Neurotrophins have multiple effects such as increasing mast cell number, basophil degranulation, up-regulation of cytokine synthesis from mast cells, macrophages and granulocytes, increasing survival of plasma cells, eosinophil activation and chemotaxis in allergic reactions (7-11).

Studies concerning the roles of neurotrophins in AR patients have mainly focused on NGF. It has been shown that NGF levels of nasal lavage fluid were higher (22) and NGF and BDNF were overexpressed in nasal tissue of AR patients (16). Raap et al. (23) showed that eosinophil apoptosis is inhibited when eosinophils are stimulated by NT-3. Recently, Gelincik et al. (2) showed that levels of NGF and TrkA receptors were higher in AR patients. These findings showed that neurotrophins may play a role in AR pathogenesis. Articles concerning the relationship between AR and neurotrophins are summarized in Table 3.

IL-5-induced eosinophils actively release mRNA for production of NGF and NT-3 (24). After the activation of Trk A,

B and C receptors of neurotrophins, which are found on eosinophils, the secretion of IL-4 from eosinophils is increased (25). After nasal provocation with an allergen in AR patients, BDNF expression in nasal mucosa and NGF expression in peripheral nerves and nasal lavage fluid are increased (26). These findings suggest that activation of neurotrophins may be an alternative pathway in AR pathogenesis.

In our study, we found that NT-3 staining levels of nasal mucosa were higher in the AR group than in the control group; this finding is similar to the literature regarding other neurotrophins (2,16,22) Increases in serum neurotrophin levels in allergic diseases has also been shown (12,16), whereas, in the study of Raap et al. (16), this increase was not statistically significant both before and after nasal provocation tests. Furthermore, it is also known that neurotrophins have autocrine or paracrine features. They may show their effects either locally, where they are synthesized, or in an adjacent site (7,21). In our study, levels of serum NT-3 were higher in the control group, but the results were not statistically significant. Also, there was no statistically significant difference between serum NT-3 levels and nasal mucosa NT-3 staining scores in the AR group. This situation may be explained by the local production of NT-3 in nasal mucosa. It may show their effects on the local site without joining the systemic circulation in AR patients. The small sample size and possibility of taking serum samples in the non-allergic season may have affected the results of our study. There was a slight sex difference between groups in our study (p=0.011), but, to the best of our knowledge, there is no known study showing the difference of serum NT-3 levels among healthy human subjects with different genders.

The limitations of our study were getting samples of serum and nasal tissues shortly after the skin prick test and the gender profile of our groups.

In conclusion, besides neurotrophins, including NGF and BDGF, whose probable effects were previously shown in AR, NT-3 might also play a role in AR pathogenesis. Additional studies including larger groups of patients with the same gender profile may be more supportive of the effect of NT-3 in the neuronal inflammation of AR.

Ethics Committee Approval: Ethics committee approval was received for this study from the Local Ethics Committee.

Peer-review: Externally peer-reviewed.

Informed consent: Written informed consent from patients was obtained in both the AR and control groups.

Author contributions: Concept - O.İ., C.Ö., T.K., G.P., Y.V., T.G., K.G.; Design - O.İ., C.Ö., T.K., G.P., Y.V., T.G., K.G.; Supervision O.İ., C.Ö., T.K., G.P., Y.V., T.G., K.G.; Materials - O.İ., C.Ö., T.K., G.P., Y.V., T.G., K.G.; Data Collection &/or Processing - O.İ., C.Ö., T.K., G.P., Y.V., T.G., K.G.; Analysis &/or Interpretation - O.İ., C.Ö., T.K., G.P., Y.V., T.G., K.G.; Literature Search - O.İ., C.Ö., T.K., G.P., Y.V., T.G., K.G.; Writing - O.İ., C.Ö., T.K., G.P., Y.V., T.G., K.G.; Critical Reviews - O.İ., C.Ö., T.K., G.P., Y.V., T.G., K.G.

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Conflict of Interest: No conflict of interest was declared by the authors.

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