Local Levels of Soluble Tumor Necrosis Factor Receptors in Patients With Allergic Rhinitis Are Regulated by Amount of Antigen

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**Objectives:** To examine the possible correlation between the amount of antigen and the level of soluble tumor necrosis factor receptor (sTNFR), and to assess its biologic significance in allergic reactions.

**Design:** Randomized control trial.

**Subjects:** Twelve volunteers with Japanese cedar pollenosis and 10 healthy volunteers.

**Interventions:** The levels of p55 sTNFR (sTNFR1) and p75 sTNFR (sTNFR2) in samples of serum and nasal epithelial lining fluid (ELF) from 12 subjects with pollenosis and 10 healthy subjects were measured 4 times (preseason, early season, midseason, and postseason) in low-(total, 415/cm² per season) and high- (total, 19935/cm² per season) pollen-count periods, and the results were compared among the 4 groups.

**Results:** In the low-pollen-count period, increased levels of sTNFR1 and sTNFR2 were observed in ELF samples from the allergic subjects during the midseason. In contrast, in the high-pollen-count period, those levels were already elevated during the preseason and reduced during the midseason. Especially, the levels of sTNFR2 in ELF samples from the allergic subjects during the midseason in the high-pollen-count period were significantly lower than those in the low-pollen-count period. Moreover, a significant negative correlation (sTNFR1, R = −0.82; sTNFR2, R = −0.73) was found between the levels of sTNFR1 and sTNFR2 in ELF samples and the scores of symptoms in the allergic subjects in the high-pollen-count period, but not in the low-pollen-count period.

**Conclusion:** In patients with pollenosis, the amounts of antigen regulate the local levels of sTNFRs, possibly inhibiting nasal allergic inflammation.

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Tumor necrosis factor α (TNF-α), which is one of the proinflammatory cytokines, is reported to be able to potentiate nasal allergic inflammation. In fact, studies have demonstrated that allergen provocation can induce a significant up-regulation of the levels of TNF-α in nasal lavage fluid from patients with allergic rhinitis. Increased expression levels of TNF receptor (TNFR) on nasal epithelial cells from patients with allergic rhinitis were also reported. These data suggest that TNF-α and TNFR may play a role in the pathogenesis of allergic rhinitis. On the other hand, p55 soluble TNFR (sTNFR1) and p75 soluble TNFR (sTNFR2) were identified as inhibitors of TNF-α-mediated inflammatory reactions in vitro and in vivo. These reports suggest the possibility that sTNFR1 and sTNFR2 could play a role as inhibitors of nasal allergic inflammation. Kato et al previously demonstrated that levels of sTNFR1 and sTNFR2 were elevated in patients with allergic rhinitis during the allergy season in the low-pollen-count period. In this study, we measured systemic and local levels of sTNFR1 and sTNFR2 together with scores of subjective symptoms in patients with seasonal allergic rhinitis as well as in healthy subjects throughout the allergy season (preseason, early season, midseason, and postseason) in both high- and low-pollen-count periods.

**RESULTS**

The airborne Japanese cedar pollen counts during the low- (total, 415/cm² per season; maximum, 47/cm² per day) and high- (total, 19935/cm² per season; maximum, 1971/cm² per day) pollen-count periods in Nagoya were reported by the Aichi Prefecture Department of Health (Figure, G...
and H). Roughly, the pollen counts were undetectably small (<1/cm²) preseason and postseason during the low-pollen-count period. A pollen count of less than 50/cm² per day was detected early season and midseason during the low-pollen-count period and preseason and early season during the high-pollen-count period. A pollen count greater than 1000/cm² per day was detected midseason during the low-pollen-count period on January 19 (preseason), February 23 (early season), March 18 (midseason), and May 20 (postseason) and during the high-pollen-count period on January 20 (preseason), February 24 (early season), March 16 (midseason), and May 25 (postseason). They were then subjected to intergroup comparative analyses. According to Kaulbach et al, urea nitrogen concentrations are invariant in plasma, interstitial and glandular fluids, and nasal epithelial lining fluid (ELF), whether or not allergic rhinitis is induced by a challenge test. Therefore, we used urea as a reliable marker for the correction of the parameters measured in nasal lavage fluid. The levels of each parameter in nasal lavage fluids were compared after the latter were multiplied by the dilution factor (=[urea]serum/[urea]nasal l.) and revised to the levels in ELF. Collections of nasal lavage fluids were conducted using the technique described by Kato et al. Subjective symptoms, which consisted of nasal blockage, secretion, and sneezing, were estimated by a questionnaire. The symptoms were graded according to the following 4-point scale: −, no symptoms; +, mild; ++, moderate; and ++++, severe. The sum of each individual’s symptom score (top score, 9 points) was tallied for estimating total individual subjective symptoms.

LEVELS OF sTNFR1 AND sTNFR2

During the low-pollen-count period, the levels of sTNFRs in ELF samples from the allergic group in the early season (sTNFR1, P<.05) and the midseason (sTNFR1, P<.01; sTNFR2, P<.01) were significantly higher than the levels of sTNFRs in ELF samples from the control group (Figure, C and E). During the high-pollen-count period, those from the allergic group were already significantly elevated (sTNFR1, P<.01; sTNFR2, P<.01) during the preseason compared with those from the control group (Figure, D and F). This elevation may have been induced by the low levels of pollen (<50/cm² per day) that were observed for several months before the preseason in the high-pollen-count period, but not in the low-pollen-count period (data not shown).

LEVELS OF SUBJECTIVE SYMPTOMS

In the allergic group, the scores of subjective symptoms midseason during the low-pollen-count period were significantly lower (P<.01) than those in the high-pollen-count period (Figure, A and B). However, there was no statistical difference between the high and low amounts of pollen in the scores of subjective symptoms during the preseason, early season, and postseason. In the control group, the scores of subjective symptoms were unchanged during the high- and low-pollen-count periods throughout the 4 season times.

PATIENTS AND METHODS

STUDY DESIGN

The allergic group (n=12; mean age, 36 years) consisted of patients with a history of Japanese cedar pollen–induced rhinitis and a radioallergosorbent test that was strongly positive solely for Japanese cedar pollen. There was no difference between the high- and low-pollen-count periods among the subjects in the allergic group, and they showed no other organic manifestations of their allergic disease during the study. The control group (n=10; mean age, 35 years) consisted of volunteers who had no histories of allergic or nasal disease. The trial was approved by the Nagoya University Branch Hospital, Nagoya, Japan, and each subject gave written informed consent before entering the study. No drugs were permitted for the allergic or control subjects during the study and for a period of 3 weeks before. In both the control and the allergic groups, a range of subjective symptoms as well as the levels of sTNFR1, sTNFR2, and urea nitrogen in samples of serum and nasal lavage fluid were examined during the low-pollen-count period on January 19 (preseason), February 23 (early season), March 18 (midseason), and May 20 (postseason) and during the high-pollen-count period on January 20 (preseason), February 24 (early season), March 16 (midseason), and May 25 (postseason). They were then subjected to intergroup comparative analyses. According to Kaulbach et al, urea nitrogen concentrations are invariant in plasma, interstitial and glandular fluids, and nasal epithelial lining fluid (ELF), whether or not allergic rhinitis is induced by a...
in ELF samples from the control group in the early season, midseason, and postseason during the high-pollen-count period. Interestingly, the levels of sTNFR2 in ELF samples from the allergic group in midseason during the low-pollen-count period were significantly higher ($P<.01$) than those during the high-pollen-count period (Figure, E and F). However, in the allergic group, the levels of sTNFR1 in ELF samples preseason ($P<.01$), midseason ($P<.01$), and postseason ($P<.05$) and the levels of sTNFR2 in ELF samples preseason ($P<.05$) during the low-pollen-count period were significantly lower than those during the high-pollen-count period.

The levels of sTNFR1 and sTNFR2 in serum samples from the allergic group were slightly lower than those in serum samples from the control group, whereas no statistical differences between the 2 groups could be found throughout the 4 season periods. These results partially correspond with previously reported data that serum levels of the soluble form of Fas (a member of the TNFR family) in samples from patients with pollinosis were significantly reduced compared with those in samples from healthy subjects. The levels of sTNFRs in ELF samples from the control group were about 20% to 25% (sTNFR1) or 3% to 5% (sTNFR2) of those in serum samples from the control group. The levels of sTNFRs in ELF samples from the allergic group were up-regulated to 80% (sTNFR1) or 20% (sTNFR2) of those in serum samples from the allergic group.

**CORRELATION BETWEEN THE SCORES OF SUBJECTIVE SYMPTOMS AND sTNFRs IN ELF SAMPLES**

A significant negative correlation ($sTNFR1, R = -0.82$ [$P<.01$]; $sTNFR2, R = -0.73$ [$P<.02$]) was found between the levels of sTNFRs in ELF samples and the scores of symptoms in the allergic group during the high-pollen-count period. We could find no statistically significant correlation between other parameters in the control and allergic groups throughout the 4 season times during either the high- or the low-pollen-count period.

**COMMENT**

We first showed that the local levels of sTNFR in the samples from allergic subjects were not different from those in samples from the healthy control subjects under undetectably small ($<1/\text{cm}^2$) antigen provocation. We then demonstrated that local levels in samples from the allergic subjects were significantly elevated during low levels ($<50/\text{cm}^2$ per day) of antigen provocation, and significantly reduced during high levels (>1000/\text{cm}^2 per day). These results suggest that the local levels of sTNFRs in patients with seasonal allergic rhinitis were biophysically regulated by the amount of antigen. Furthermore, we demonstrated a significant negative correlation between the levels of sTNFRs in ELF samples and the scores of symptoms in the allergic subjects under high but not under low levels of allergen provocation. These results suggest the possibility that locally produced sTNFRs under low levels of allergen provocation might be consumed to protect against severe allergic inflammation by high levels of allergen provocation. Reports indicating that intratracheal administration of sTNFR inhibited acute pulmonary inflammation induced by endotoxin in the respiratory system partially support our hypothesis and, in conjunction with it, may encourage the topical
administration of sTNFRs as a therapy for allergic rhinitis in the future. However, further study is essential to clarify the biological function of sTNFR in allergic inflammation.

In short, we demonstrated that the local sTNFRs levels were controlled by the amount of antigen and that they were possibly involved in the regulation of allergic inflammation.

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REFERENCES


