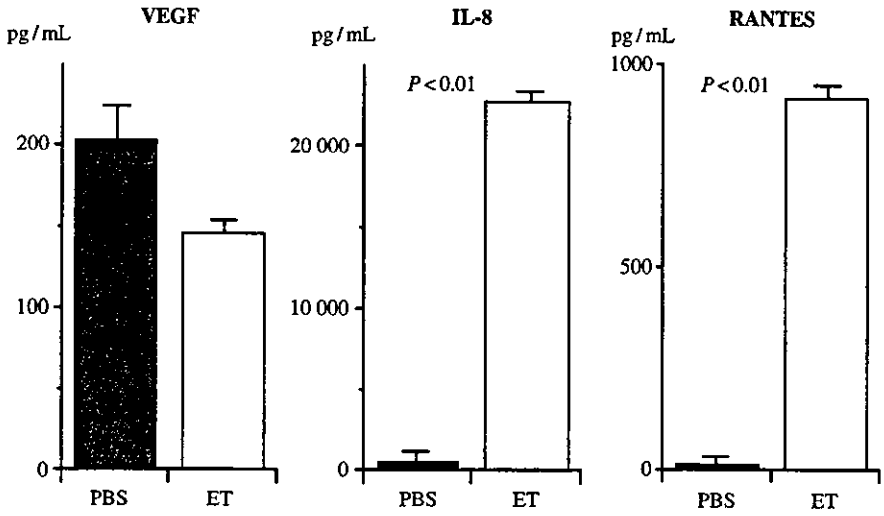


**Fig. 2.** Cytokine production from cultured human nasal fibroblasts after stimulation with endotoxin purified from nontypeable *Haemophilus influenzae*. PBS, phosphate buffered saline (control); ET, endotoxin. Reprinted with kind permission from Kurono [37].

before and repeatedly after allergen challenge showed induction of radiographic changes, primarily increases of mucosal oedema and/or opacification, in most patients positive for nasal responses. These responses were accompanied by increased pressure in the maxillary sinuses, suggesting the occurrence of severe nasal blockade. On the other hand, patients who were negative to the provocation tests did not show increased thickening of the mucosal membrane of the maxillary sinuses. These results demonstrate a role of AR in the pathogenesis of CS. However, the study did not indicate that radiographic changes in the maxillary sinuses were induced only by severe nasal blockade: the allergens inoculated into the nose may have infiltrated into the sinuses through natural ostium and hence caused allergic inflammation of sinus mucosa.

To clarify the direct effects of nasal blockade on sinus pathology, radiographic findings of maxillary sinuses of patients undergoing nasal septoplasty were compared before surgery and after removing the nasal tampon packed in the middle meatus for 3 days [10]. Radiographic opacity of maxillary sinuses was observed in most patients only by nasal blockade after surgery. Sinusitis induced in animal models of AR might also be due to nasal blockade, as eosinophil infiltration was not observed in sensitized animals and mononuclear cells were predominant in sinus effusions of sensitized as well as control animals [18]. These findings indicate that natural sinus ostium blockade might be associated with sinus pathology but not allergic reaction in sinuses. Stenosis or blockade of natural sinus ostium is speculated to induce hypoxia in maxillary sinuses because sinus mucosa is composed of respiratory epithelium. Ganjian et al. [20] demonstrated that nasal obstruction and maxillary ostial occlusion affect the ratio of oxygen and carbon dioxide in the maxillary sinus of New Zealand white rabbits. Corey et al. [21] suggested that hypoxia is an important predisposing factor for human maxillary mycosis. Matsune et al. [10] investigated partial oxygen pressure in maxillary sinuses and found that it was significantly lower in inflamed than normal sinuses irrespective of the presence or absence of AR. These findings indicate that hypoxia can be induced in paranasal sinuses by the blockade of natural sinus ostium and is associated with pathological changes in sinus mucosa.

Recently, it has been demonstrated that hypoxic condition enhances the production of vascular endothelial growth factor (VEGF), a protein associated with angiogenesis and vascular permeability [22]. When nasal fibroblasts isolated from nasal polyps were cultured under hypoxic condition, production of VEGF was remarkably increased while that of IL-8 and RANTES was not affected (Fig. 3).

These results suggest that type I allergic reaction in the nostril induces nasal and natural sinus ostium blockade, which causes hypoxia in paranasal sinuses, then, hypoxic condition causes oedema of sinus mucosa via enhanced production of VEGF. Hence a variety of factors other than type I allergic response are associated with the pathogenesis of AS.

## Relation between AR and OME

Epidemiological studies have shown that children with AR frequently have comorbid OME. Jordan [23] reported that 91 of 123 (74%) patients with OME were found to have AR, and Draper [24] reported that 52.3% of patients with AR were complicated with OME. However, these observations were made prior to the discovery of IgE and the examinations used for the diagnosis of AR are not clear. Several clinical studies have been performed based on widely accepted diagnostic criteria of AR in order to investigate the precise relationship between AR and OME. Tomonaga et al. [2] reported that in children aged 5–8 years the ratio of complication of AR in OME patients was 50%, while that of OME in AR patients was 21%. In contrast, the incidence of AR and OME in control subjects was 19% and 8%, respectively. Bernstein and Reisman [25]

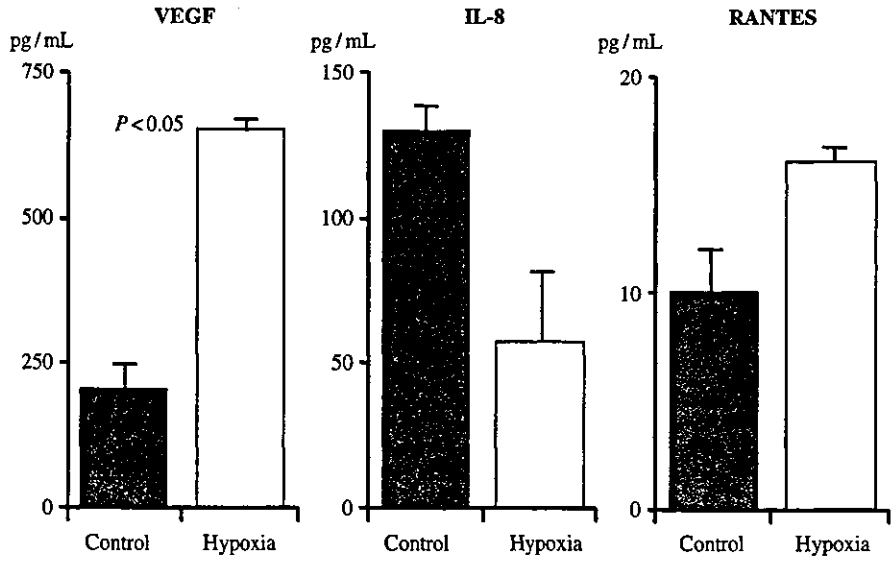


**Fig. 3.** Cytokine production from human nasal fibroblasts cultured under hypoxic condition. Reprinted with kind permission from Kurono [37].

studied the number of eosinophils in nasal secretion and peripheral blood, skin test for allergen, and serum IgE level of infants with OME and reported that 24% of patients were complicated with AR. These findings suggest significant aetiological or pathogenetic relationships between these two diseases.

### *Type I allergy in the middle ear*

Eosinophil infiltration and increased levels of IgE are characteristic findings of type I allergy. King [26] demonstrated that eosinophils were detectable in 5–10% of mucoid MEE but not in serous MEE. Other studies have shown that very few eosinophils are present in MEE and middle ear mucosa of patients with OME complicated with AR, although eosinophil infiltration may be notable in nasal secretion and nasal mucosa [23]. Phillips et al. [27] observed increased levels of IgE in MEE compared with serum IgE, although the accuracy of the measurement method employed has been criticized [28]. Moreover, results obtained by paper radioimmunosorbent test failed to support the concept of allergy as a major causative factor in OME, as the effusion-to-serum ratio of IgE levels was $< 1$. Mogi et al. [4, 5] studied specific IgE antibody activities against mites in MEE and suggested that the production of MEE is not due to direct allergic reaction to allergen in the mucous membrane lining the middle ear cavity. In contrast, Hurst et al. [7, 8] indicated a significant relation between allergic reaction and production of MEE. They found that 86% of atopic OME patients had elevated levels of effusion eosinophil cationic protein compared with controls and proposed the hypothesis that middle ear mucosa, like that of the rest of the upper respiratory tract, is capable of inducing allergic response.

Yamashita et al. [29] investigated histological changes of the tympanic cavity and eustachian tube of guinea pigs on OVA challenge into the tympanic and nasal cavities following systemic sensitization with the same antigen. They found remarkable allergic responses in the eustachian tube and tympanic cavity following antigen challenge directly into the tympanic cavity but not when treated intranasally. This suggests that allergic reaction in the nose is not associated directly with that of middle ear and eustachian tube. Furthermore, as no formation of antigen-specific IgE antibodies in the sensitized animals was demonstrated, the observed development of OME might be attributable to IgG-mediated reactions rather than IgE-mediated type I allergy.

To investigate the role of type I allergy in OME, Miglets [30] passively sensitized squirrel monkeys with human serum containing reaginic antibodies to ragweed pollen and observed the development of OME after direct inoculation of ragweed pollen into the middle ear from the pharyngeal orifice of the eustachian tube. MEE was produced 4 days after the inoculation of pollens and there were predominant polymorphonuclear leucocytes in MEE. This indicated that histological changes in the middle ear may have been induced by type I allergic reaction. On the basis of these findings, the middle ear was pronounced an allergic 'shock organ'. Doyle et al. [31] also investigated the production of MEE in the tympanic cavity of rhesus monkeys following passive sensitization with pollen-allergic human serum and repeated challenge with pollen antigens via the nose and eustachian tube. They failed to find MEE and inflammatory changes in the middle ear, although it was demonstrated that the pollens reached the tympanic cavity.

Tomonaga et al. [32] created an animal model of AR by passive sensitization of guinea pigs with serum containing IgE antibodies against dinitrophenyl (DNP) followed by intranasal challenge with DNP–OVA. The allergic reaction in the nose induced noticeable infiltration of eosinophils and mast cells as well as oedema in the mucous membrane lining the nose, nasopharynx and orifice of eustachian tube

but not in the tympanic cavity. In contrast, direct antigen challenge into the tympanic cavity evoked similar histological changes in the membrane lining the tympanic cavity. However, no macroscopic presence of MEE was demonstrated. These findings indicate that inhaled antigen cannot reach the tympanic cavity due to the physiological barrier of eustachian tube and that type I allergy is not a causal factor of OME, even if the middle ear is an allergic shock organ.

## AR and function of the eustachian tube

To investigate whether nasal allergic reactions interrupt the clearance of MEE, Mogi et al. [6] established an animal model of OME complicated with AR and found that the number of ears with MEE was apparently greater in animals challenged intranasally with allergic antigen than in controls after inducing OME by intratympanic inoculation with immunocomplex. Labadie et al. [33] also tested the hypothesis that allergen presentation to the middle ear causes functional disruption of the eustachian tube predisposing to the development of OME. They showed clearly that allergic rats had larger amounts of MEE compared with nonallergic controls. Tomonaga et al. [32] investigated the mechanism whereby clearance of MEE was interrupted by the provocation of nasal allergy, and found that the opening pressure of the eustachian tube significantly increased after intranasal antigen challenge. In humans, remarkable swelling and hypersecretion in the mucosa surrounding the pharyngeal orifice as well as eustachian tube dysfunction were observed after intranasal histamine challenge [2]. We also demonstrated that eustachian tube function is disturbed in patients with AR or OME compared with in nonallergic subjects (Table 2). Walker et al. [34] reported similar results. These findings suggest that AR causes morphological as well as functional changes in eustachian tube and is associated indirectly with the pathogenesis of OME.

### *Effects of antiallergic medicine on OME complicated with AR*

Suzuki et al. [35] examined the effects of the oral anti-allergic drug azelastine hydrochloride (AZ) in patients with OME accompanying AR. A total of 53 patients were randomized to receive either AZ 2 mg plus S-carboxymethyl cysteine (SCMC) 750 mg or SCMC 750 mg only (controls) daily for 8 weeks. Those receiving AZ had superior improvements in both nasal and ear symptoms compared with the control group. Moreover, the global improvement ratings of nasal symptom were significantly correlated with those of ear symptom in the AZ group.

**Table 2.** Eustachian tube function (mean ± SD) in patients with OME and AR and in nonallergic subjects by sonotubometry

| Diagnosis | *n* | Mean age (years) | Duration (ms) | Sound pressure (dB) |
|---|---|---|---|---|
| OME | 14 | 6 | 319 ± 165 | 9 ± 6 |
| AR | 22 | 7 | 358 ± 189 | 10 ± 7 |
| Nonallergic | 7 | 6 | 397 ± 117 | 14 ± 8 |

Beneficial effects of anti-allergic medicine against OME complicated with AR were confirmed by experimental studies using animal models [36]. After oral treatment with AZ, the number of animals having MEE was significantly reduced in a dose-dependent manner in the group of animals with OME and AR but not in those without AR, suggesting that AZ promotes the evacuation of MEE from the tubotympanum in this OME animal model associated with AR. Moreover, the findings provide evidence that an anti-allergic drug may contribute indirectly to the improvement of OME complicated with AR by promoting the evacuation of MEE from tubotympanum disturbed by type I allergic reaction in the nasopharynx surrounding the orifice of eustachian tube.

## Conclusions

The presence of AR disturbs the function of sinus ostium and eustachian tube and affects the prognosis of both CS and OME. In the treatment of patients with such upper respiratory tract infections complicated with AR, the association of AR with the pathogenesis of these diseases should be taken into consideration and special attention paid to establishing an appropriate remedial plan.

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