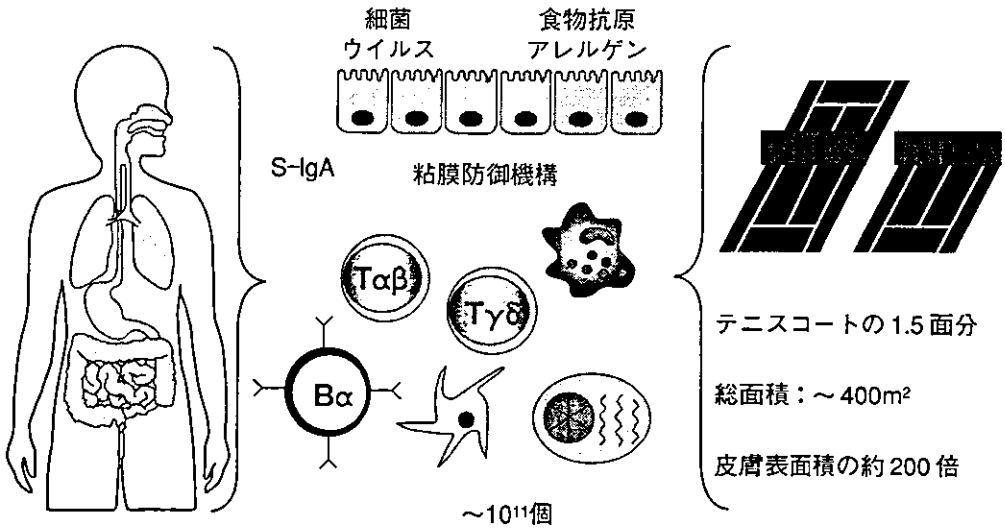

図1　第一線の生体防御バリアーとしての粘膜免疫機構
ヒトの体は極論すればチューブ状構造物の集合体であり，その内腔を覆う粘膜の表面積はテニスコート1.5面分に相当する。天文学的数字にのぼる多様な病原微生物が侵襲する呼吸器・消化器の粘膜には人体の有する約50%の免疫担当細胞が集結している。

得られる微生物感染症に限られているが，現在世論が強く望んでいるのは，エイズや結核をはじめとする，反復再感染が常態である多くの粘膜標的感染症のワクチンの実用化である。また，理想的なワクチンが具備すべき特徴として，①被接種者すべてに効果があり，その効果の永続性が高いこと，②接種が容易で，副作用がなく安全であること，③製造や品質管理が容易で，かつコストが安いこと，などをあげることができる。マラリアや破傷風を除く，現在世界のレベルで人類の脅威となっている大部分の病原微生物感染症は，呼吸器，消化器，泌尿生殖器などを覆う粘膜面を介して感染が成立する。幸い粘膜組織には生体防御の最前線として前記病原微生物をはじめとする数多くの異物と対峙し，生体の免疫学的恒常性の維持に寄与する人体最大の免疫組織が配備されている（図1）[1,2]。

この粘膜での特異免疫誘導・制御の機構を介してワクチン抗原を投与し，粘膜組織を中心に感染防御免疫を付与するための製剤が，狭義の粘膜ワクチンである。粘膜ワクチンはその投与経路により，経口，点鼻，点眼ワクチンなどと呼称される。経口的に投与されたワクチンの多くは消化器粘膜に局在するgut-associated lymphoid tissue（GALT）において特異免疫応答を誘導する[3-6]。

わが国で実用に供されているポリオ生ワクチンを経口的に投与した場合は，小腸粘膜組織に分泌型IgA（S-IgA）を中心とした感染防御体液性免疫応答とCTLを中心とした感染防御細胞性免疫応答が誘導されることが知られている。また，流血中にもポリオウイルスに対するIgGを中心としたウイルス中和抗体が誘導され，結果的に粘膜組織のみならず全身末梢免疫系を含めた2段構えの防御免疫を誘導できる。すなわち，感染成立部位である粘膜面における水際での感染阻止に加えて，感染成立後のウイルス血症や小児麻痺の発症阻止まで期待できる（図2）。

さらに，粘膜免疫循環帰巣システム（common mucosal immune system）を介することで，ワクチンを投与した粘膜局所のみならず，遠隔の粘膜組織にまでS-IgAやCTLを中心とした特異免疫応答を誘導することが知られている。操作性，安全性などの観点でも従来の注射によるワクチン接種より格段に優れており，有効性，安全性に秀でた守備範囲の広い理想的な予防・治療ワクチンといえよう（表1）。米国ではすでに点鼻インフルエンザワクチンの実用化が進み，その使用が始まっている。

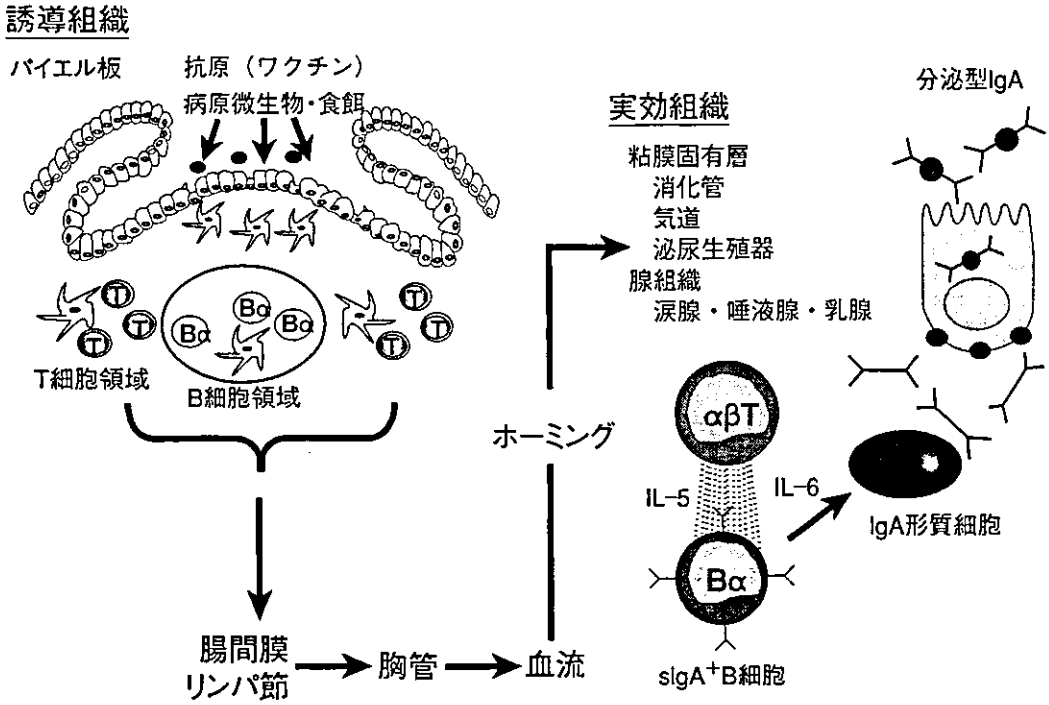

図 2 粘膜免疫機構：誘導組織と実効組織から構成された粘膜免疫誘導のための帰巣循環システム（CMIS）
消化管に取り込まれ，パイエル板に到達した粘膜ワクチンはM細胞と呼ばれる特殊な腸管の上皮細胞を介して，M細胞の直下に局在する粘膜系樹状細胞に送達される。粘膜系樹状細胞内での抗原の処理ならびに提示の過程，およびその帰結としての粘膜系樹状細胞の活性化の程度が，その後に生じるワクチン抗原特異的な感染防御免疫応答の運命を決定する。M細胞から取り込まれた抗原によって感作されたB細胞はリンパ濾胞内で分化成熟し，傍濾胞領域で感作されたT細胞とともに腸間膜リンパ節，胸管を経て血液循環に入り，再び近傍ないしは遠隔の粘膜固有層や腺組織に帰還（ホーミング）する。固有層に移動したB細胞は二量体のIgAを産生する形質細胞へ最終分化する。その後，上皮細胞を逆行輸送する際にpoly Ig受容体（分泌片）の付加を受け，最終的には二量体の分泌型IgAとして粘膜表面へ放出される。パイエル板樹状細胞によって活性化された$CD4^+$ T細胞から分泌されるサイトカインによってパイエル板$sIgM^+$ B細胞は$sIgA^+$ B細胞に免疫グロブリンのアイソタイプを変換する。さらに粘膜固有層において，$sIgA^+$ B細胞はTh2型$CD4^+$ T細胞から分泌されるサイトカイン（IL-5，IL-6）によってIgA形質細胞へ最終分化する。また，Th1型$CD4^+$ T細胞は上皮細胞からのpoly Ig受容体（分泌成分）の産生に寄与する。

表 1 なぜ粘膜ワクチンなのか

利　点	実用化に向けて
・粘膜系と全身系免疫による2段構えの感染防御の誘導	・抗原量の検討
・分泌型IgAの誘導：病原体の粘膜への付着阻止・病原体の中和	・粘膜免疫調節因子・アジュバントの開発
・粘膜系傷害性T細胞（CTL）の誘導	・より効率的な抗原投与法・送達法の確立
・安全性が高い	
・操作性がよい（投与が簡便）	
・経済的である（費用対効果）	
・副作用が少ない	

IV.　粘膜免疫を非特異的に強化するアジュバント

経粘膜的にワクチン抗原を投与すると，粘膜のみならず脾臓に代表される全身系免疫担当組織において2段構えの抗原特異的免疫応答を誘導できること，さらに操作性，安全性などの観点においても注射による免疫より格段に優れていることが経験的に示されている。しかしながら不活化ワクチン・精製ワクチンを単独で粘膜を介して接種した場合は，粘膜組織固有の解剖学的ないしは生理学的な性状に起因する，ワクチン抗原の物理化学的な不安定性，免疫担当組織への不確実な抗原送達などの弱点により，期待したほどの特異免疫を粘膜組織に付与することができないのが実状であった。そこで，このような粘膜の特性に附随する弱点を克服し，粘膜を介した不活化・精製ワクチン抗原の送達の効率や免疫誘導効果を上げるために各種の工夫が試みられてきた。

最近，様々な細菌毒素由来の物質に粘膜免疫を介して粘膜局所のみならず全身系免疫をも非特異的に高める作用があることが明らかになってきた。その一つがコレラ毒素の粘膜アジュバントとしての利用である[7]。コレラ毒素をアジュバントとして粘膜ワクチンに併用すると，当該ワクチン抗原に対するS-IgAを主体とした粘膜系と血清IgGを主体とした全身系の両特異体液性免疫がワクチン抗原の単独投与に比べて著しく亢進することが示された。また，Th1型やCTLなどの細胞性免疫応答の亢進も粘膜組織のみならず全身組織においても確認された。このアジュバントとしての作用は蛋白質抗原のみならず，糖質，脂質，ウイルス，細菌など，幅広い抗原で認められた。

V.　粘膜アジュバントのヒトへの応用

ヒトへの応用に向けて，コレラ毒素に附随する毒素本来の活性を消失した安全な粘膜アジュバントの開発が積極的に試みられている[8]。コレラ毒素の毒素活性を担うADP-リボシルトランスフェラーゼの活性中心に変異を加えた変異型コレラトキシンは毒素活性を消失するものの，アジュバント活性は維持されていることが明らかになっている。

この無毒化変異型コレラトキシンの粘膜アジュバントとしての有用性については多種多様なワクチン，蛋白質抗原に対する免疫増強効果の検討が行われた。たとえば，肺炎双球菌次世代ワクチン抗原として期待される菌体表層蛋白質PsPAワクチンと無毒化変異型コレラトキシンを混合し，経鼻免疫する実験系で検証されている[9]。その結果，免疫動物の粘膜組織のみならず全身系において，PsPAに特異的な免疫応答の増強が観察された。さらに，その感染防御効果を致死量の肺炎双球菌の感染実験で評価したところ，変異毒素との混合ワクチン接種群において約80%のマウスが肺炎双球菌感染による致死を免れることが明らかになった。今後，この無毒化コレラトキシンのヒト粘膜アジュバントとしての実用化が期待される。さらに近年では，コレラトキシンと病原性大腸菌由来の易熱性毒素の有効成分を人為的に共存させたキメラ型粘膜アジュバントの開発が進められている。

VI.　新たな粘膜ワクチンキャリアー：膜融合リポゾーム

粘膜を介したワクチンの送達に関する前述した弱点を克服する新たなアプローチとして，センダイウイルスの膜融合能をリポゾームに付与したfusogenic liposome（膜融合リポゾーム）の応用が進められている。膜融合リポゾームは膜表面に存在するセンダイウイルス由来のエンベロープ蛋白質を利用し哺乳動物細胞に吸着・融合することで，リポゾームに封入した抗原を効率よく細胞質に導入することができる[10]。センダイウイルスの属すパラミキソウイルスは本来，上気道粘膜に感染するウイルスであることからも，この方法は経鼻ワクチン・吸入ワクチンの開発を考慮した場合，理にかなった抗原投与法といえる。モデル抗原として卵白アルブミン（OVA）を封入した膜融合リポゾームを経鼻免疫し，その後の免疫応答を検討したわれわれの実験成績によると，経鼻免疫マウスの粘膜関連リンパ組織ならびに脾臓の$CD4^+$ T細胞は試験管内における再度のOVA刺激によりIFN-γをはじめとするTh1型サイトカイン，IL-4，IL-5，IL-6などのTh2型サイトカインをバランスよく産生していること，また抗原特異的体液性免疫応答では上記の所見をよく反映して，

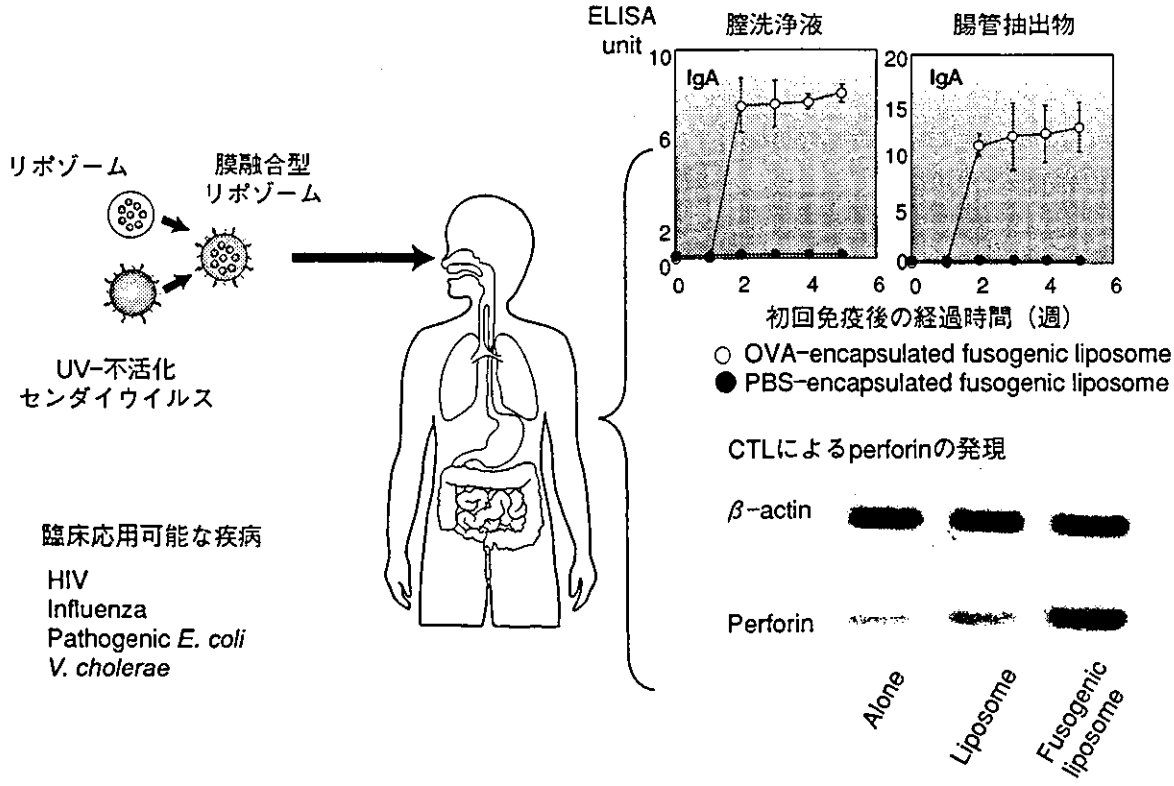

図 3 膜融合型リポゾーム経鼻粘膜ワクチンの開発
われわれは粘膜を介したより効果的なワクチン抗原の送達をめざして，センダイウイルスの膜融合能に着目し，これをリポゾームに付与した膜融合リポゾームを考案した。膜融合リポゾームは膜表面に存在するセンダイウイルス由来のエンベロープ蛋白質を利用し哺乳動物細胞に吸着・融合することで，リポゾームに封入した抗原を効率よく細胞質に導入することができる。この膜融合リポゾームに卵白アルブミン（OVA）を封入し，粘膜ワクチンとしての効果を評価した。その結果，ワクチン封入膜融合リポゾームを免疫した群では，エイズウイルスの感染が考えられる組織，腸管と生殖器などの遠隔の粘膜組織に抗原特異的な S-IgA の誘導と CTL 活性の誘導が認められた。

鼻腔洗浄液と糞便中に OVA 特異的 IgA 抗体の誘導が，また血清中では OVA 特異的 IgG 抗体産生の増強がみられた（図 3）[11]。さらに膜融合リポゾームワクチン経鼻免疫マウスでは，脾臓，腸間膜リンパ節，頸部リンパ節などの臓器・組織においてワクチン抗原特異的な細胞傷害活性を有する $CD8^+$T 細胞の誘導も観察された。

以上の結果より，膜融合リポゾームを用いて抗原を経粘膜的に投与することで粘膜面と全身の両組織において抗原特異的な細胞性ならびに体液性免疫応答を誘導できることから，膜融合リポゾームは新規の経粘膜ワクチンキャリアーとしての有用性が明確に示された。現在では，当該膜融合リポゾームは HIV ウイルスの感染予防と治療を目的とした粘膜ワクチンの投与媒体としての可能性についても検討が進んでいる。たとえば，エイズワクチン候補抗原の一つである HIV gp160 抗原を膜融合リポゾームに封入したものを経鼻免疫することで，効果的に HIV gp160 特異的免疫応答が粘膜系・全身系免疫の両方に誘導されることがわかってきた。

おわりに

近年，基礎免疫学と臨床免疫学が有機的に連携・融合した“粘膜免疫学”という新たな免疫学パラダイムの進展があり，生体防御の最前線における免疫応答の本質的な理解とその破綻に起因した疾病の病因・病態の解明，さらに合理的な治療・予防法の開発に関する研究が精力的に展開されている。この粘膜免疫学研究には既存の概念や方法論では未だに克服されていないエイズ，結核，新型インフルエンザなどの難治性の粘膜感染症の画期的な制御法の確立が託されている。

今後，新たな経口ワクチン・経鼻ワクチンに代

表される粘膜ワクチンが実用化されることによって，数多くの感染症の克服に限りない夢と希望を約束するかもしれない。たとえば米国では，噴霧式の体にやさしい経鼻インフルエンザワクチン（商品名 FluMist®）の実用化が進み，医療現場での使用が始まった。わが国でも粘膜を介して発症する感染症において注射によるワクチンから飲むワクチン・吸うワクチンへ転換することが期待されている。

さらに一歩進んで，食べるワクチンの研究も開始されている。たとえば，B型肝炎ワクチンを植物に寄生するウイルスを巧みに利用してバナナに作らせる研究や，病原性大腸菌ワクチンや齲蝕ワクチンを馬鈴薯に発現させる研究が欧米で進められている[12]。食べるワクチンは発展途上国などの経済的な事情により現行のワクチンを利用できない地域で威力を発揮するかもしれない。

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The role of allergic rhinitis in upper respiratory tract inflammatory diseases

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Summary

The number of patients with allergic rhinitis (AR) is increasing. Furthermore, patients with otitis media with effusion (OME) and chronic sinusitis (CS) are frequently complicated with AR. These findings suggest that AR has an impact on the pathogenesis of both OME and CS. The direct and indirect influence of AR on OME and CS was investigated by clinical and experimental studies to clarify the mechanism by which type I allergic reaction is associated with OME and CS. Clinical findings of patients with OME or CS complicated with AR were analysed and compared with those of nonallergic subjects. Samples such as sinus effusions and middle ear effusions (MEE) were collected from the patients and infiltration of inflammatory cells and concentrations of inflammatory cytokines determined. In addition, previous reports discussing the relationship between AR and OME or CS are reviewed. Eosinophil infiltration and oedema were remarkable in paranasal sinus mucosa of patients with CS complicated with AR, suggesting the presence of type I allergic reaction in sinus mucosa. However, there was little evidence of eosinophils in sinus effusions. Endotoxin was frequently detected in sinus effusions of patients with CS having AR as well as suppurative CS. Hypoxia was also considered an important factor inducing sinus pathology. Eosinophils and IgE antibodies in MEE were not increased in OME patients with AR. Anti-allergic medicine was effective in OME patients complicated with AR and improvement of nasal symptoms significantly correlated with that of ear symptoms. AR might be directly and indirectly associated with the pathogenesis of OME and CS.

Keywords allergic rhinitis, chronic sinusitis, eosinophil, eustachian tube, hypoxia, IgE, otitis media with effusion, vascular endothelial factor

Introduction

Otitis media with effusion (OME), chronic paranasal sinusitis (CS) and allergic rhinitis (AR) are the most common upper respiratory tract diseases in children [1]. Furthermore, AR has been implicated as a major causative factor of OME and CS due to the increased number of patients with AR complicated by OME and CS [2]. However, the precise role of AR in the pathogenesis of OME and CS is controversial.

Senturia et al. [3] reported that there is no direct scientific evidence to support the contention that middle ear effusion (MEE) is due to allergic reaction. Recent studies also demonstrated that IgE-mediated allergic reaction is not an aetiological factor but rather a persisting factor of OME due to disturbance of the clearance of MEE by the eustachian tube [4–6]. On the other hand, the presence of type I allergic reaction has been reported [7, 8] and anti-allergic drugs have proved efficacious in the successful treatment of OME in allergy-free patients [9].

Patients with AR frequently show a pathological shadow in X-ray examination of the sinuses despite a lack of infectious symptoms in nostrils such as purulent rhinorrhoea [10, 11]. Such patients are usually diagnosed as having allergic sinusitis (AS), although the definition and the pathogenesis of this disease have not been defined clearly [12, 13].

In the present study, we discuss the role of AR in the pathogenesis of OME and CS based on the results of our experiments and present a review of the literature on these issues.

Relation between AR and CS

Radiological opacity is frequently found in paranasal sinuses of patients with AR. A retrospective study of AR patients in our clinic showed that 67% of those aged < 16 years and 44% aged ≥ 16 years had some radiological opacity in maxillary sinuses [10]. Although the mechanism

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inducing sinus pathology in patients with AS is not fully understood, type I allergic response, infection and natural ostium blockade are considered the chief factors associated with the pathogenesis of this entity [14].

Type I allergic reaction in paranasal sinuses

Because remarkable eosinophilic accumulation can be observed in paranasal sinus mucosa as well as in nasal mucosa, the influence of type I allergic inflammation might be considered to be associated with the mucosal pathology of CS. Ogata et al. [15] investigated the histological differences in maxillary sinus mucosa between noninfectious CS complicated with AR and suppurative CS without AR and found that the numbers of goblet cells and eosinophils were significantly increased in the former condition. Basal membrane hyperplasia and oedema of lamina propria were also remarkable in noninfectious CS complicated with AR in comparison with suppurative CS without AR. Furthermore, the same histological findings were induced in the maxillary sinus mucosa of patients with AR caused by house dust by stimulating the mucosa with that antigen during sinus surgery [15]. These findings indicate that paranasal sinus is one of the target organs for type I allergic reaction and that type I allergic inflammation in paranasal sinuses might be associated with sinus pathology of patients with CS complicated with AR. However, the ostium connecting the nostril and paranasal sinus is too small for antigens such as mites and pollen to enter into the sinuses [16]. Moreover, autoradiographic study showed that sinus pathology does not change during the pollen allergy season, indicating that the sinus pathology was not associated with direct antigenic stimulation of sinus mucosa [13].

Infection in paranasal sinuses

Because neutrophils are frequently contaminated in nasal and sinus secretions obtained from patients with AS or suppurative CS, microbial infection seems to be involved in the pathogenesis of AS [17]. To investigate the characteristics of inflammatory cells infiltrating into paranasal sinuses of patients with AS, sinus secretions of child patients with AS complicated with OME were collected by aspiration during middle ear ventilation tube insertion under general anaesthesia and the cellular components examined. In all samples neutrophils but not eosinophils were observed (Table 1). In contrast, eosinophils were predominant in nasal secretions of patients with AR. Shirasaki et al. [18] developed an animal model of AR by sensitizing guinea pig with ovalbumin (OVA) and compared the inflammatory cells infiltrating into nasal and sinus mucosa. They found that mononuclear cells were predominant in the smears of sinus effusion from sensitized animals, although marked eosinophil infiltration and increased numbers of goblet cells were observed in nasal mucosa.

Table 1. Cell infiltration in maxillary sinus effusions obtained from child patients with allergic sinusitis

Case no.	Age (years)	Antigen	Eosinophils	Neutrophils
1	14	House dust	—	+++
2	5	House dust	—	++
3	6	House dust	—	+
4	6	House dust	—	+

Endotoxin is a cell wall component of Gram-negative bacteria and its presence in sinus secretion is considered indicative of infection of such bacteria into paranasal sinuses. In a preliminary study, we measured the concentration of endotoxin in sinus effusions and found that endotoxin was frequently detectable in sinus secretions of patients with CS. However, there was no significant difference in the concentrations of endotoxin in sinus secretion between AS and suppurative CS patients (Fig. 1). Moreover, when cultured human nasal fibroblasts isolated from nasal polyps were stimulated with endotoxin purified from nontypeable *Haemophilus influenzae*, the production of IL-8 and RANTES was remarkably enhanced (Fig. 2). As these cytokines act as chemokines specific for neutrophils and eosinophils, endotoxin present in sinus secretion of patients with AS may induce infiltration of not only neutrophils but also eosinophils into sinus mucosa.

Collectively, the above findings suggest that bacterial infection might be associated with the onset of sinus pathology in patients with AS as well as in those with suppurative CS.

Blockade of natural sinus ostium

If type I allergic reaction is related directly or indirectly to sinus pathology, the severity of AR might be correlated with the intensity of sinus opacity on X-ray examination. Pelikan et al. [19] investigated the role of AR in CS without an air–fluid level by nasal provocation tests with various inhalant allergens. Maxillary sinus radiographs performed

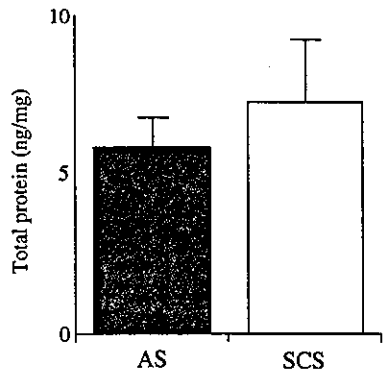

Fig. 1. Concentration of endotoxin in sinus effusion obtained from patients with allergic sinusitis (AS) and suppurative chronic sinusitis (SCS). Reprinted with kind permission from Kurono [37].

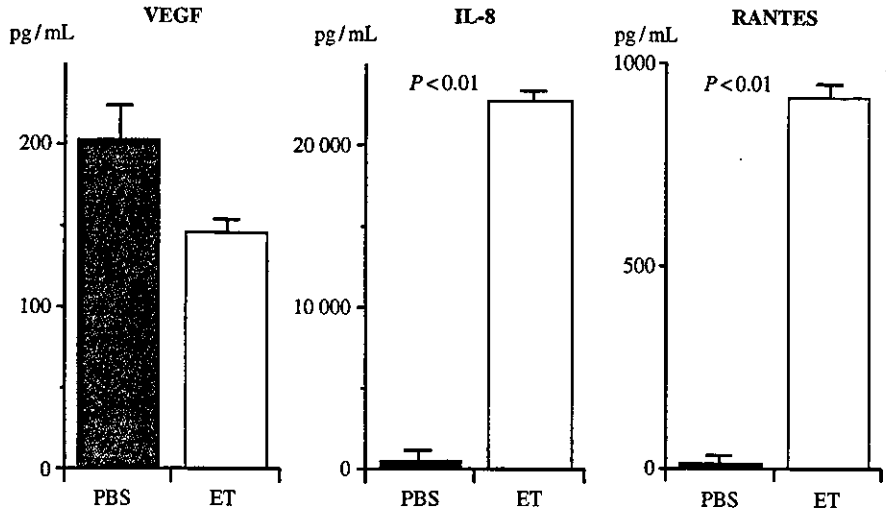

Fig. 2. Cytokine production from cultured human nasal fibroblasts after stimulation with endotoxin purified from nontypeable *Haemophilus influenzae*. PBS, phosphate buffered saline (control); ET, endotoxin. Reprinted with kind permission from Kurono [37].

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]

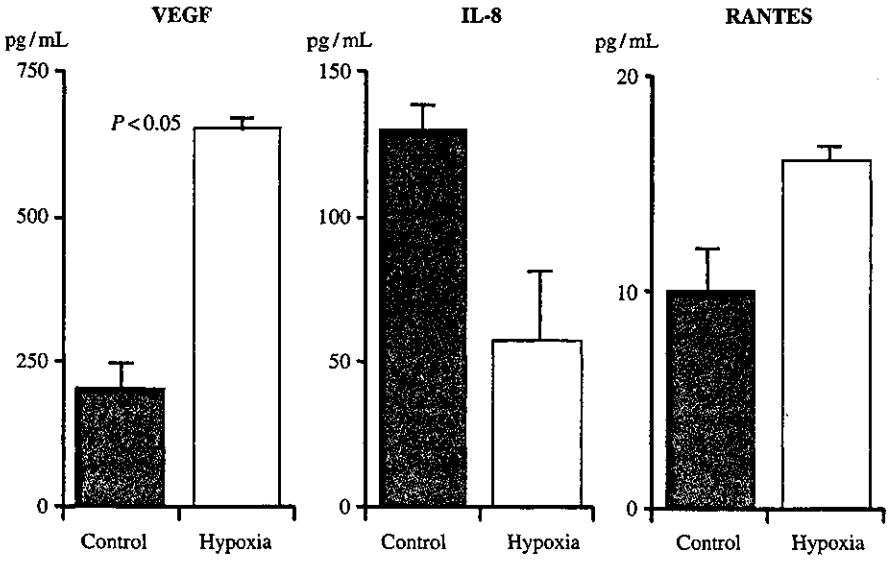

Fig. 3. Cytokine production from human nasal fibroblasts cultured under hypoxic condition. Reprinted with kind permission from Kurono [37].

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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