

The role of local allergy in the nasal inflammation

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Abstract Local allergic inflammation (LAI) is recognized recently. ‘entropy’ was used to define LAI, which was positively correlated with allergen provocation testing, local sIgE up-regulation, inflammatory mediator secretion, and a lack of systemic allergy. The study of LAI is in its infancy and focuses mainly on the respiratory system. It is closely related to nasal inflammation and plays important roles in patients with nonallergic rhinitis (NAR), nonallergic chronic sinusitis with nasal polyps (CRSwNP), and nonallergic fungal rhinosinusitis (NAFRS). Based on studies using nasal allergen provocation testing, 40–57% of patients with NAR exhibited positive results and could be diagnosed as local allergic rhinitis. Total IgE and common airborne allergen-sIgE were up-regulated in eosinophilic CRSwNP patients compared to noneosinophilic CRSwNP patients and healthy controls, possibly due to local allergic inflammation. Some researchers also found that the level of local sIgE was increased in patients with NAFRS; they suggested that local allergic inflammation occurs in NAFRS. Studies of LAI will increase our understanding of nasal inflammation and help to establish novel treatments. However, the diagnosis of local allergic inflammation is complex due to the lack of convenient detection methods. The relationship between local allergic inflammation and systemic allergic inflammation is unclear, and an appropriate treatment for local allergic inflammation is required.

Keywords Local allergy · Rhinitis · Rhinosinusitis · IgE · Nasal allergen provocation testing

Introduction

Allergic inflammation is an allergen-induced T cell-, B cell-, mast cell-, eosinophil-, and basophil-mediated response that is mediated by specific IgE antibodies (sIgE). Multiple cytokines participate in allergic inflammation, which causes systemic and local dysfunction and which is affected by an individual’s genetic makeup. Allergic inflammation occurs in three stages: sensitization, immediate phase reactions, and late phase reactions. During the sensitization stage, allergens activate B cells, which synthesize sIgE. Subsequently, the sIgE combine with high-affinity IgE receptor (FcεR) proteins located on mast cells and basophils. During the immediate phase, the organism has its second exposure to the allergen, which combines with the sIgE-FcεR on mast cells and basophils, causing them to release multiple bioactive factors. This process can last anywhere from several minutes to 2–3 h [1]. The late phase begins 4–6 h after the onset of the immediate phase and continues for 18–24 h. During this stage, Th2 cells, eosinophils, and basophils infiltrate the tissue and release interleukin (IL)-4, IL-5, IL-9, and IL-13 [2].

To diagnose an allergic reaction, a skin prick test (SPT) or serum sIgE test is performed. Allergic inflammation can occur in multiple tissues and organs, including the nasal cavity, skin, and lungs, and it can cause systemic inflammation [3]. Allergic inflammation, including asthma, allergic rhinitis (AR), atopic dermatitis, eosinophilic gastroenteritis, and food allergies affect ~10% of the global population.

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Local synthesis of IgE

In 1966, IgE was discovered in serum [4]. IgE is the least abundant immunoglobulin in serum and is distributed primarily in peripheral tissues. It is secreted by active B cells with the assistance of T follicular helper cells [5, 6] and has a short half-life [7]. Following activation by allergens and T cells in peripheral lymphoid tissues, B cells translocate to follicles where they proliferate and form germinal centers. Other B cells move to the periphery of such follicles, proliferating and differentiating into plasma cells [8]. Free IgE combines with FcεRI, a high-affinity IgE receptor found on mast cells, basophils, and dendritic cells [7, 9]. In allergic diseases, including asthma and AR, the local synthesis of IgE by B cells and plasma cells increases. KleinJan et al. [10] found that 4% of B cells and 12–19% plasma cells expressed IgE in the nasal membrane of AR patients compared to <1% in healthy controls.

In healthy individuals, serum and bone marrow IgE concentrations are low [11]. In AR patients, however, the concentration of IgE in local tissues is higher than that in serum, and may be a source of serum IgE [12]. Eckl-Dorna et al. [13] found that the concentration of sIgE in peripheral blood mononuclear cells was below that in nasal secretions; they also suggested that sIgE in peripheral blood are secreted into local tissues.

Recent studies have suggested that IgE is synthesized in local tissues during allergic inflammation [14, 15]. Ishizaka et al. [16] found that IgE-positive cells were mainly located in lymphoid follicles of the respiratory and digestive tracts. Allergic diseases are common in the upper and lower respiratory tracts, and several studies have shown that IgE is synthesized locally in those areas [17, 18]. IgE was found in both the sputum and bronchial secretions of allergic asthma patients [15], and Chvatchko et al. [19] detected germinal center formation and IgE synthesis in the lungs of mice following allergen stimulation. In addition, Wilson et al. [20] found allergen-sIgE in bronchial lavage fluid following allergen provocation. The nasal cavity is the gate of the airways, and it provides multiple opportunities for contact with allergens. Multiple cell types induce and synthesize allergen-sIgE in nasal membranes, and related cytokines (e.g., IL-4, IL-13, and the ligand of CD40) are secreted in these areas [21, 22].

Local IgE synthesis in the nasal region is typically analyzed using nasal secretions or lavaged fluids; however, some researchers have used nasal tissues. In 1975, Huggins et al. [23] discovered local IgE synthesis in the nasal mucous membranes of AR patients. More recently, Sensi et al. [24] used an in situ incubation technique to show that the level of sIgE increased faster in the nasal region than in serum. In addition, KleinJan et al. [10] used immunohistochemistry to

show that the number of local IgE-positive B cells increased in nasal membranes, while Zürcher et al. [25, 26] used an in vitro assay to show that IL-4 and the ligand of CD40 stimulated IgE production by B cells. Smurthwaite et al. [12] used enzyme-linked immunosorbent assays (ELISAs) to show that nasal pollen-sIgE increased in and out of pollen season in individuals with pollen allergies. The level of local IgE is also up-regulated in nonallergic CRSwNP, which may be induced by nonclassical allergic pathways [27]. Bachert et al. [27] showed that *Staphylococcus aureus* enterotoxins (SEs) act as superantigens that induce the polyclonal synthesis of local sIgE, and this up-regulation may be the source of IgE in CRSwNP.

Superantigens and local IgE

Superantigens are specialized antigens that contact T cell receptors through major histocompatibility complex II molecules rather than through antigen-specific loci. Superantigens activate 25% of T cells, while only 0.1% of T cells are activated via classical allergic inflammation. In addition, these factors activate B cells, produce IL-4, IL-5, and IL-13, and cause eosinophilic inflammation and the polyclonal synthesis of local sIgE [28, 29]. Superantigens act locally, without systemic influences, and are important causes of local increases in IgE antibodies. Currently, the best-known superantigens are SEs. Six SE subtypes exist: SEA, SEB, SEC, SED, SEE, and toxic shock syndrome poison-1 (TSSP-1) [30]. They play a role in many diseases, including severe asthma, chronic obstructive pulmonary disease, CRSwNP, atopic dermatitis, and food poisoning [31]. Using ELISAs, Tanaka et al. [32] found that the levels of SEA-sIgE and SEB-sIgE were elevated in the serum of patients with severe asthma. Using the Phadia ImmunoCAP system, Ong et al. [33] also found that the level of serum SE-sIgE was elevated in patients with atopic dermatitis.

SEs are regarded as etiological factors in CRSwNP and are responsible for elevated local IgE levels in that disease; however, this remains controversial. Bachert et al. [34] first found SEA- and SEB-sIgE in nasal polyps, suggesting a role for SEs in the pathogenesis of CRSwNP. Using flow cytometry, Tripathi et al. [35] also found that SEA-, SEB-, and TSSP-1-positive T cells were increased in the nasal polyps of CRSwNP patients. Moreover, SEA-, SEC-, and TSSP-1-sIgE were elevated in the homogenate supernatant of nasal polyps in CRSwNP patients [30], and SE-sIgE, total IgE, and eosinophil cationic protein were shown to be up-regulated in nasal polyps [36]. The up-regulation of local IgE in CRSwNP patients was unrelated to the results of SPT and serum sIgE tests [27]; however, that finding

may have been caused by SEs. In a study of 31 CRSwNP patients and 13 cases of chronic sinusitis without nasal polyps (CRSSNP), Niederfuhr et al. [37] failed to identify SEs in cases of chronic sinusitis. Thus, whether elevated local IgE levels in CRSwNP patients are caused by superantigens or local allergic inflammation remains unknown.

Local allergic inflammation

Recent investigations using nasal allergen provocation testing (NAPT) showed correlations with nonallergic rhinitis (NAR). In such cases, local allergen-sIgE levels were elevated, while serum levels of sIgE were lower. In the previous studies, ‘entopy’ was used to define local allergic inflammation (LAI), which was positively correlated with NAPT, local sIgE up-regulation, inflammatory mediator secretion, and a lack of systemic allergy [38–40]. NAPT and the examination of local sIgE are the primary methods for diagnosing local AR (LAR), which is rhinitis with LAI [41]. NAPT is complex and only one allergen is examined during each test; thus, it is difficult for NAPT to be used for large-scale diagnoses of LAR. Recently, Rondon et al. [42] used NAPT with multiple aeroallergens to assess 25 cases of LAR. The pathological changes that occur during LAI are similar to those observed during systemic inflammation, and include the local synthesis of sIgE, activation of mast cells, infiltration by eosinophils, and secretion of inflammatory mediators. However, no standard methods exist to test local levels of sIgE.

The study of LAI is in its infancy and focuses mainly on the respiratory system. Using the Phadia ImmunoCAP-100 and ImmunoCAP ISAC systems, Prathap et al. [14] found that local allergen-sIgE were elevated in the serum and bronchial mucous membranes of patients with nonallergic asthmas, suggesting that the up-regulation of local sIgE was caused by LAI. In addition, Takhar et al. [43] found that the level of local IgE in bronchial tissues was increased in allergic and nonallergic asthma patients, while Balzar et al. [44] found that IgE combined with mast cells were increased in the lower airway, but not related to systemic IgE.

Local allergy in chronic rhinitis

Chronic rhinitis affects 20–40% of the global population, and its prevalence is increasing. Chronic rhinitis is divided into two subtypes: AR and NAR [45]. AR is caused by exact allergens and is induced by IgE; it presents as nasal obstructions, rhinorrhea, itching, and sneezing, and it generates a positive SPT or serum sIgE test result. NAR

has similar clinical features to AR; however, it is not induced by IgE or allergens. NAR affects ~200 million people worldwide and generates negative SPT and serum sIgE test results [46].

Elevated levels of local sIgE, inflammation due to Th2 and eosinophilic responses, and positive results on NAPT are common among AR patients. Based on studies using NAPT, 40–57% of patients with NAR exhibited positive results [39, 47]. Using immunohistochemistry, Powe et al. [48] reported positive results from the inferior turbinate in 3 of 10 cases. In 20 cases of NAR, Wierzbicki et al. [49] found 9 cases where NAPT identified common allergens, while Rondon et al. [47] studied nasal lavage fluids from 50 NAR and 30 AR patients and identified similar cytokines in both cohorts. They also found that 54% of NAR patients were positive for house dust mite markers and 22% were positive for house dust mite-sIgE. Using NAPT, Carney et al. [50] found that 85% of 23 NAR cases were positive for house dust mites. Some researchers defined the rhinitis with LAI as the LAR or ‘entopy’ [40, 51]. However, it is still controversial [52].

LAR is a unique form of chronic rhinitis; it is neither classical AR nor NAR. Thus, a portion of patients diagnosed with NAR or chronic rhinitis of unknown etiology may have LAR [53]. The symptoms, duration, severity, and complications of LAR are similar to those of AR. LAR can affect adults and children, with a higher incidence in children [54, 55]. The morbidity of LAR in children is uncertain [53]; symptoms include nasal obstruction, rhinorrhea, itching, and sneezing, which are often present with conjunctivitis and asthmas [56–58]. One study showed that 51.1% of LAR cases occurred with conjunctivitis, and 18.8% occurred with asthmas [59].

The mite is the most common allergen in LAR patients [59], and whether LAR can evolve into AR is controversial [60]. The lack of understanding about LAR stems from a lack of studies following large sample sizes over long periods of time. A 2007 study that used SPT to reexamine 180 NAR cases from 2000 to 2004 found that 24% were positive results [61]. Thus, LAR may evolve into AR. However, in another study in which 194 LAR cases were reexamined after 10 years and compared to 130 healthy controls [59], no differences were observed between the groups. Thus, LAR may be a unique form of rhinitis without any relationship to AR [59].

The diagnosis of LAR is mainly based on NAPT and local concentrations of sIgE [62]. Rondón et al. found that pollen-sIgE and ECP levels elevated in the nasal lavage fluids of 30 cases LAR patients after the pollen-NAPT [63]. Lopez et al. found that house dust mite-sIgE and ECP levels increased in the nasal secretions of 40 cases LAR patients after the house dust mite-NAPT [64]. However, performing both NAPT and local tests for sIgE is difficult.

Thus, recent studies have used the basophil activation test (BAT) to diagnose LAR. Basophils are important during the immediate phase of allergic inflammation. One study found that the BAT provided a 50% diagnosis rate with higher sensitivity than tests for local sIgE [65]. The BAT is also more convenient than NAPT. Nasal cytology is a simple and safe diagnostic procedure that allows to assess the normal and pathological aspects of the nasal mucosa, by identifying and counting the cell types and their morphology [66]. It can identify the normal cells (ciliated and mucinous), the inflammatory cells (lymphocytes, neutrophils, eosinophils, and mast cells), bacteria, or fungal hyphae/spores [66]. Nasal cytologic evaluation may aid to differentiate LAR from other forms of rhinitis [67]. Nasal Th2 IgE-mediated inflammation was confirmed by cytometric evaluations of nasal lavage fluid in LAR patients [56]. In LAR patients after NAPT, mast cells and eosinophils were immediately activated, with the nasal release of the characteristics: pro-inflammatory mediators, tryptase, and ECP [41].

The treatments for LAR and AR are similar and include topical glucocorticoid and antihistamine drug treatments. The effects of immunotherapy on LAR are unclear; Rondon et al. [68] found that subcutaneous immunotherapy relieved its symptoms while improving performance on objective tests of patients with LAR. While an ovalbumin-induced mouse model has been developed for AR, no animal models have been established for LAR. Toward this end, Kato et al. [69] sensitized and challenged the mouse nasal cavity with ragweed pollen to induce LAR, while Liang et al. [70] administered a low dose of ovalbumin allergens to induce LAR in mice.

Local allergy in chronic sinusitis (CRS)

CRS refers to chronic inflammation (longer than 12 weeks) of the nasal cavity and sinusitis. CRS affects millions of individuals worldwide, and it can lead to serious complications [71]. The disease is divided into the two subgroups, CRSwNP and CRSsNP, based on whether nasal polyps are present (respectively). The subtypes exhibit different pathogenic mechanisms and clinical manifestations, with CRSsNP presenting as fibroses and Th1-related inflammation [72]. CRSwNP has a more complex pathogenesis, including allergies, inflammation, infections, anatomic abnormalities, genetic factors, superantigens, and bacterial biofilms [73]. Notably, systemic allergy is important in the pathogenesis of CRSwNP in Caucasians [74].

Elevated local IgE levels are characteristic of CRSwNP. In the polyps of CRSwNP, local IgE levels increase and B cells differentiate into plasma cells [75]. The levels of local sIgE also increase, becoming similar to those found in

serum [76]. The elevation of local IgE was thought to be caused by systemic allergy; however, recent studies showed a lack of evidence for systemic allergy. Local levels of *Alternaria*-sIgE are also increased in nasal polyps, which are related to eosinophilic inflammation but not systemic allergy [77]. Local IgE was found to be up-regulated in the lavage fluid of CRSwNP patients, without the elevation of serum IgE [78], and some researchers have suggested that local elevations in IgE might be caused by SEs. Superantigens activate large numbers of T and B cells and produce local IgE; however, the pathway is different from that for classical allergic inflammation. One study showed that SE-sIgE increased in nasal polyps and could induce polyclonal IgE antibody formation [31]. In fact, Zhang et al. [79] found that the levels of SEB-sIgE increased in nasal polyps, with a concomitant up-regulation of local airborne allergen-sIgE in serum. Conversely, patients with CRSsNP manifest Th1-related inflammation without IgE and SE-sIgE up-regulation [80].

Local IgE in nonallergic CRSwNP are induced by SEs and local allergic inflammation. Excluding superantigens, local allergic inflammation may be the main reason for the elevation of local IgE in nonallergic CRSwNP. Baba et al. [81] found that the IgE levels in local tissues increased in eosinophilic CRSwNP, with no evidence for systemic allergy or SEs. Similarly, Zhang et al. [82] found that local IgE levels were elevated in eosinophilic CRSwNP patients without systemic allergy but with local allergic inflammation. Cao et al. [83] studied 20 cases of suspected eosinophilic CRSwNP and 29 cases of noneosinophilic CRSwNP, and found that many were actually noneosinophilic. Total IgE and common airborne allergen-sIgE were up-regulated in eosinophilic CRSwNP patients compared to noneosinophilic CRSwNP patients and healthy controls, possibly due to local allergic inflammation and mast cell activation.

Local allergy in noninvasive fungal rhinosinusitis

Noninvasive fungal rhinosinusitis is a common disease that is divided into two subtypes: allergic fungal rhinosinusitis (AFRS) and nonallergic fungal rhinosinusitis (NAFRS). AFRS is a unique form of sinusitis that is more common in Caucasians and in the southeastern USA [84]. AFRS is an IgE-induced type I allergy that presents as a positive result for fungal cultures. Moreover, it has a unique imaging manifestation and produces eosinophilic mucin without fungi and nasal polyps [85, 86]. AFRS treatment requires surgery, immunotherapy, and anti-allergic therapies. Recent studies suggested that local sIgE were produced in the local tissues of patients with AFRS, including the sinuses, inferior turbinate [82], and nasal lavage [87].

Notably, NAFRS has the same clinical manifestations as AFRS, but without systemic allergy. Some researchers have found that the level of local sIgE was increased in patients with NAFRS [88–90]; they suggested that local allergic inflammation occurs in NAFRS.

Conclusions and future prospects

Local allergic inflammation is a disease that is becoming increasingly recognized. It is closely related to nasal inflammation and plays important roles in patients with NAR, nonallergic CRSwNP, and NAFRS. Studies of local allergic inflammation will increase our understanding of nasal inflammation and help to establish novel treatments. However, the diagnosis of local allergic inflammation is complex due to the lack of convenient detection methods. The relationship between local allergic inflammation and systemic allergic inflammation is unclear, and an appropriate treatment for local allergic inflammation is required.

Compliance with ethical standards

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Conflict of interest All authors declare that they have no conflict of interest.

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