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Comparison of Basophil Histamine Releasability between Atopic and Nonatopic Asthmatics

To compare the mediator releasability between atopic and nonatopic asthmatics, we measured basophil histamine releasability (BaHR) using a calcium-ionophore A23187 and anti-IgE in 137 subjects who were treated at Seoul National University Hospital. Subjects were categorized into atopic (group AA, n=77) or nonatopic asthmatics (group NA, n=32), or normal controls (group NC, n=28). Serum total IgE levels were determined and correlation with BaHR was assessed. Anti-IgE-induced maximal BaHR in groups AA, NA, and NC was 41.0 ±3.2, 23.1±4.5, and 16.8±3.8, respectively (mean±SE, %). Anti-IgE-induced BaHR in group AA was significantly higher than that in groups NA and NC ($p<0.05$). Calcium ionophore A23187-induced maximal BaHR was 43.1±2.8, 40.8±4.4, and 50.5±5.2, respectively (mean±SE, %), and there was no significant difference among the groups. Serum total IgE level correlated significantly with anti-IgE-induced maximal BaHR ($r=0.281$, $p<0.01$) but not with that induced by calcium ionophore A23187. In conclusion, IgE receptor-related BaHR is higher in atopic asthmatics than in nonatopic asthmatics, and this increased BaHR in atopics is significantly associated with increased serum total IgE level.

Key Words : *Basophils; Histamine Release; Asthma; Hypersensitivity, immediate*

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INTRODUCTION

Allergic disorders are characterized pathophysiologically by enhanced IgE production, increased mediator release from inflammatory cells, and hypersensitivity of target organs. It is well known that IgE plays an important role in the development of allergic diseases and that IgE production is enhanced in the majority of patients with bronchial asthma (1). This phenomenon is known as atopy, but all of atopics do not develop allergic diseases and some asthmatics are nonatopic. These findings indicate other factors contribute to the pathogenetic mechanism in development of asthma as well. The release of chemical mediators from inflammatory cells depends on the intrinsic property of the cell (2, 3), and it has been suggested that increased mediator releasability as well as atopy is an important factor in the development of bronchial asthma. Measuring the amount of histamine release from basophils is used to evaluate mediator releasability. Basophil is an important effector cell in allergic inflammation, and moreover, it also has a function controlling allergic inflammation (4, 6).

The release of cytokines and chemical mediators from inflammatory cells give rise to chronic allergic inflammation. It has been proven that in individuals with an allergic disease, the blood level of chemical mediators such as histamine is increased, and spontaneous or IgE-mediated histamine release is enhanced (7, 9). Some studies have suggested, however, that there is no difference in histamine releasability between an allergic and nonallergic patient, and that because of in vivo desensitization, this in fact decreases (10). This discrepancy seems to be caused by differences in method and the stimuli used for evaluating mediator releasability. In studies of asthmatics it has been reported that spontaneous and antigen-induced histamine release from basophils is increased (11, 13), though in the pathogenesis of bronchial asthma, the role of mediator releasability per se is still controversial. Some studies showed allergen-induced basophil histamine release is increased in allergic asthmatics, but it is due to existence of allergen specific IgE and increased allergen-IgE coupling signal.

The aim of this study is to compare mediator releasability in atopic and nonatopic asthmatics. To evaluate this independently of the amount of allergen-IgE coupling signal, we used anti-IgE and calcium ionophore A23187 as basophil-releasing stimuli. Both are known to induce histamine release regardless of IgE level and IgE-mediated and non-IgE-medi-

ated histamine releasability can thus be evaluated.

MATERIALS AND METHODS

Subjects

A total of 137 outpatients at the Department of Pediatrics, Seoul National University Hospital were selected for this study. They were divided into three groups: 1, atopic asthmatics (Group AA, N=77); 2, nonatopic asthmatics (Group NA, N=32); and 3, nonatopic controls (Group NC, N=28). Atopy was determined by a skin prick test (see below), and was deemed to exist when there was a positive response to one or more of ten allergens. For all subjects a modified questionnaire was used; this was developed from the Respiratory Disease Questionnaires of the American Thoracic Societies (14); bronchial asthma was diagnosed when a patient with asthmatic symptoms showed reversible airway obstruction or bronchial hyperresponsiveness. A patient was considered to show asthmatic symptoms if at least two of four such symptoms (paroxysmal cough, wheezing, nocturnal dyspnea, and dyspnea at rest) were positive on questionnaires; reversible airway obstruction was defined as a 15% increase in forced expiratory volume in one second (FEV1) after bronchodilator trial. Drugs such as theophylline or beta-2 agonist which can interfere basophil histamine releasability were discontinued at least for two wk before measurement.

Skin prick test

Skin prick tests were performed in all cases using 10 commercially available inhalant allergens (Allergopharma, Germany) containing house dust mites (*D. pteronyssinus, D. farinae*), fungi, tree pollens, grass pollens, mugwort pollen, ragweed pollen, animal epithelium, and cockroach. Histamine, at a concentration of 1 mg/mL and 50% glycerin in diluent (Allergopharma Co., Germany), was used as positive and negative controls, respectively. Fifteen min after pricking, the wheal size was compared with that when histamine was used. The response to each allergen was judged positive when a wheal was larger than that of histamine.

Methacholine bronchial provocation test

When asthmatic symptoms were present but reversible airway obstruction was not proven, bronchial hyperresponsiveness was evaluated using methacholine bronchial provocation test. The tests were carried out by modifying of Chai' s method (15). FEV1 was measured with a computerized spirometer (Microspiro-HI, Chest, Japan), and the highest value of triplicate FEV1 was adopted. Methacholine (Sigma Chemical, St Louis, Mo., U.S.A.) at concentrations of 1.25, 2.5, 6.25, 12.5, and 25 mg/mL was prepared by dilution with buffered saline solution. A Rosenthal-French dosimeter (Laboratory for Applied Immunology, Baltimore, Md., U.S.A.) was used to deliver the aerosol, generated from a Devilbiss 646 nebulizer. Subjects with asthmatic symptoms inhaled five inspiratory capacity breaths of buffered saline and increasing concentrations of methacholine until FEV1 fell by more than 20% of the postsaline value or the highest concentration was reached. The largest value of triplicate FEV1 at 90 and 180 sec after each inhalation was adopted for analysis, and the concentration of methacholine which provoked a 20% fall in FEV1 (PC20-Methacholine) was calculated. Bronchial hyperresponsiveness was considered positive when PC20-Methacholine was less than 25 mg/mL.

Serum total IgE level

Serum total IgE levels were determined by enzyme-linked immunosorbent assay (ELISA), using a peroxidase-conjugated mouse anti-human IgE (Southern Biotechnology Associates Inc., Birmingham, AL., U.S.A.). This antibody is specific to ε heavy chain of IgE molecule. Polypropylene 96-well microtitre plates (Falcon) were precoated overnight at 4℃ with mouse monoclonal anti-IgE (Sigma Chemical Co., St. Louis, MO.,U.S.A.) in carbonate buffer of 1: 3000 titer, and washed three times with 10 mM phosphate buffered saline containing Tween-20 (0.05%-Tween-20-PBS, pH 7.4). After washing, 3% bovine serum albumin in 0.05%-Tween-20-PBS was added and the plate was incubated for one hr to eradicate nonspecific background reaction; this was followed by three washes with 0.05%-Tween-20-PBS and 100 μL of serum, diluted tenfold, were added to each well in duplicate for two hr incubation. After another three washes, horse radish peroxidase (HRP)-conjugated anti-human IgE (optimally diluted at 1:1000 in 0.1% BSA-0.05%-Tween-20-PBS) was added to each well and incubated for one hour at room temperature. After five washes, 100 μL of o-phenylene-diamine dihydrochloride peroxidase substrate (Sigma) was added to each well for one hr and the reaction was terminated by the addition of 100 μL of 3 M H_2SO_4.

Optical density (OD) was determined at 492 nm in the Ceres 900™ ELISA microtiter plate reader (Bio-Tek Instruments Inc., U.K.). Using the OD of serially diluted standard serum, a graph of concentration versus OD was plotted, and on the basis of the graph, total IgE concentrations were calculated.

Basophil histamine releasability (BaHR)

Peripheral blood leukocyte isolation

Twenty milliliters of heparinized peripheral blood was collected from the antecubital vein of the subject involved and

mixed with a solution consisting of 2 mL of 0.1 mM EDTA and 5 mL of 6% dextran-2% dextrose-0.9% saline. This was followed by incubation for 90 min at room temperature. To obtain a pellet, supernatant containing plasma, leukocytes, and thrombocytes was transferred to another tube and centrifuged at 4℃ at 300 G for 8 minutes; the pellet was washed twice with 10 mL of PIPES buffer containing 4 mL of 0.1 M EDTA. Finally, 5 mL of leukocyte suspension was prepared using PIPES-ACMD buffer (pH 7.4) containing 0.03% albumin, 0.1 M Ca^{++}, 0.1 M Mg^{++}, and 1% dextrose.

Histamine release by anti-IgE and calcium ionophore A23187

After 0.2 mL of leukocyte suspension was added to 0.7 mL of PIPES-ACMD buffer, 0.1 mL of different concentrations of histamine-releasing stimulus were challenged for 15 min at 37℃. Supernatants were obtained after centrifugation at 4℃ at 700 *g* for 15 min and stabilized with 0.1 mL of 55% TCA; this was followed by freezing at -70℃ for histamine assay.

Spontaneous histamine release was measured using PIPES-ACMD buffer instead of stimulating agent, and total histamine release was measured after cell lysis. As a challenging stimulus, two different agents, goat anti-human IgE and calcium ionophore A23187 (both from Sigma) diluted with PIPES-ACMD buffer at three different concentrations (anti-IgE, 1:1000, 1:100, 1:10; calcium ionophore, 1 mM, 3 mM, 10 mM) were used; the former was for the evaluation of IgE receptor-mediated histamine release, and the latter for non-IgE receptor-mediated histamine release.

Histamine assay

Automated fluorospectrometric assay was used to quantitate the amount of histamine released. After alkalinization of the solution, histamine was extracted with butanol and liquified by 0.1 N HCl. Liquified histamine was condensed with 0.025% o-phthalaldehyde and stabilized by 0.1 N phosphoric acid. Using a fluorometer (primary filter 355 nm, secondary filter 455 nm) fluorescence was determined, and histamine releasability was calculated as shown.

$$\text{BaHR}^{*}\ (\%) = \text{Net Histamine Release} / (\text{THR}^{**}\text{-SHR}^{\dagger}) \times 100$$
$$= (\text{IHR}^{\dagger\dagger}\text{-SHR}) / (\text{THR-SHR}) \times 100$$

BaHR^{*} basophil histamine releasability; THR^{**}, total histamine release; $\text{SHR}^{\dagger}$, spontaneous histamine release; $\text{IHR}^{\dagger\dagger}$, induced histamine release.

Maximal histamine releasability (%) was defined as the highest value of BaHR found at three different concentrations of each stimulus.

Statistical analysis

Data were expressed as mean±SE. The statistical significance of means comparison was determined by ANOVA and an unpaired t test; to compare the relationship between independent continuous variables, regression analysis was performed. A p-value of less than 0.05 was considered significant.

RESULTS

Characteristics of subjects

The mean age of group AA, NA, and NC was 9.7±4.3, 8.5±3.4, and 9.6±3.8 years, respectively; there was no significant difference between the groups, nor was there a difference in the male to female ratio. Mean logarithmic values of serum total IgE levels were 2.64±0.05, 2.13±0.10, and 1.65±0.11, respectively; the mean of group AA was greater than that of group NA and NC, which were similar (Table 1).

Anti-IgE and calcium ionophore A23187-induced BaHR

Table 2 shows spontaneous and anti-IgE and calcium ionophore A23187-induced histamine releasability of the groups at each concentration of stimuli. There was no significant difference in spontaneous histamine releasability among the groups. Maximal histamine releasability, defined as the highest value of BaHR at three different concentrations of stimuli, was compared between the groups.

The means of anti-IgE-induced maximal BaHR in group AA, NA and NC were 41.0±3.2, 23.1±4.5, and 16.8±3.8, respectively. The anti-IgE-induced maximal BaHR of group AA was significantly higher than that of group NA and NC ($p<0.05$), which were similar (Fig. 1). The calcium ionophore A23187-induced maximal BaHRs of group AA, NA, and NC were 43.1±2.8, 40.8±4.4, and 50.5±5.2,

Table 1. Subject Characterstics

Group*	AA	NA	NC	Total
Number	77	32	28	137
Age (yr, Mean±SE)	9.7±4.3	8.5±3.4	9.6±3.8	9.4±4.0
Sex ratio (M:F)	2.4:1	1.1:1	1.4:1	1.8:1
Log[IgE (IU/mL)] (Mean±SE)	2.64±0.05†	2.13±0.10	1.65±0.11	2.36±0.05

*AA, atopic asthma; NA, nonatopic asthma; NC, nonatopic control group. †Mean log[IgE] of group AA was higher than group NA and NC. ($p<0.05$). There was no significant difference in age and sex ratio among groups.

Table 2. Means of spontaneous, anti-IgE-induced, and calcium ionophore-induced BaHR of the groups at each concentration of the stimuli

Group	AA (mean±SE,%)	NA (mean±SE,%)	NC (mean±SE,%)	Total (mean±SE,%)
Spontaneous BaHR	5.45±0.5	4.53±0.4	5.23±0.8	5.24±0.3
Anti-IgE				
1:1000	20.1±2.5*	9.02±2.6	6.08±3.8	14.7±1.9
1: 100	31.8±3.1*	17.1±3.5	13.6±2.9	24.6±2.3
1:10	38.8±4.1*	21.8±5.4	16.4±4.2	30.3±4.3
Calcium ionophore				
1 mM	8.81±2.2	7.14±2.2	11.4±4.1	8.95±1.7
3 mM	15.2±2.4	14.3±3.3	19.9±4.6	16.0±2.0
10 mM	42.5±2.6	40.1±4.9	49.2±4.7	43.3±2.3

AA, atopic asthmatics; NA, nonatopic asthmatics; NC, normal controls, *significantly higher than the other groups ($p<0.05$)

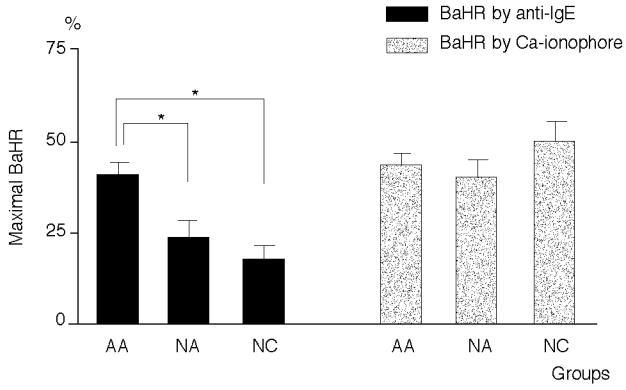

Fig. 1. Maximal basophil histamine releasability by anti-IgE and calcium ionophore A23187. BaHR:basophil histamine releasability; AA, atopic asthma; NA, nonatopic asthma; NC, nonatopic control group; *Anti-IgE induced histamine releasability of the AA group was significantly different to that of the NA and NC groups ($p< 0.01$).

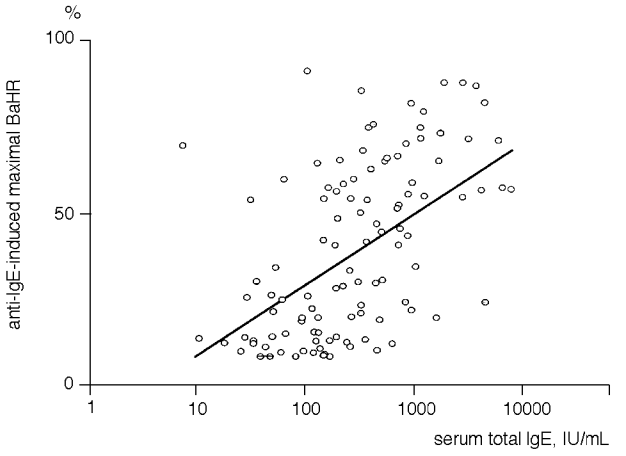

Fig. 2. Relationship between anti-IgE-induced maximal basophil histamine releasability and serum total IgE. BaHR, basophil histamine releasbility; $r_s=0.281$, $p=0.0001$

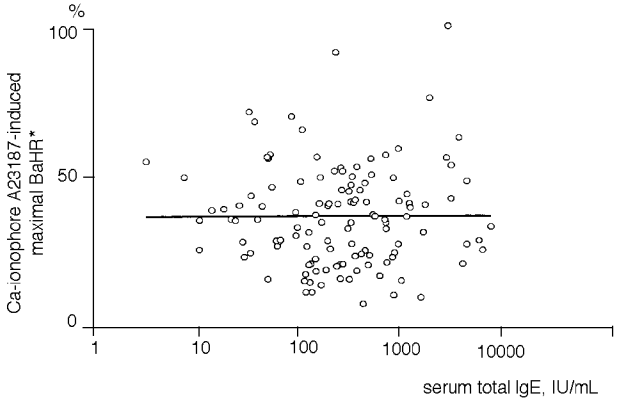

Fig. 3. Relationship between calcium ionophore induced maximal basophil histamine releasability and serum total IgE. *BaHR, basophil histamine releasability; $r_s=0.0003$, $p=0.85$

respectively; there were no significant differences between the three groups (Fig. 1).

Relationship between histamine releasability and serum total IgE

To evaluate the relationship between histamine releasability and serum IgE level, simple linear regression analysis was performed (Fig. 2, 3). Serum total IgE level correlated significantly with anti-IgE-induced basophil histamine releasability ($p<0.01$, r=0.281) but not with that induced by calcium ionophore A23187 (r=0.0003, $p=0.85$).

DISCUSSION

The concept of "mediator releasability" arose in the 1970s, when Lichtenstein and Conroy suggested that in the

pathogenesis of allergic disorders, not only the amount of allergen-IgE coupling signal, but also the intrinsic property of the cell responding to the signal is important (2). Allergic inflammatory reactions involve the participation of many different cells. Peripheral blood basophils and tissue mast cells, for example, play an important role in allergic diseases by releasing potent inflammatory mediators such as histamine, leukotrienes, and prostaglandins upon cross-linking of the membrane-bound IgE by an allergen (16).

The basophil is a more responsive cell than the mast cell. It releases mediators in response not only to IgE-dependent secretogogues but also to other stimuli such as complements, formylated bacterial products, cytokines, histamine releasing factors, low-molecular-weight peptides, hyperosmolar solutions, and lipids (17). The basophil is so sensitive that it releases histamine at 100 fold lower concentrations of anti-IgE than does the mast cell. Two kinds of stimuli induce histamine release from a basophil: IgE mediated and non-IgE mediated. Allergens and anti-IgE induce histamine release via high affinity IgE receptors (FcεR-I) on the cell surface, and non-IgE mediated stimuli such as complements, low molecualr weight peptides and lipids induce histamine release via non-IgE mediated pathways. In this study, to evaluate the mechanism of IgE-mediated and non-IgE-mediated histamine release, we measured basophil histamine release after stimulation with anti-IgE and calcium ionophore A23187, respectively.

Our present study demonstrated that anti-IgE induced basophil histamine releasability was higher in atopic asthmatics than in nonatopics or nonasthmatics, but non-IgE (calcium ionophore A23187)-mediated releasability did not differ between any group. This finding indicates that an IgE-mediated mechanism of mediator release plays an important role in the pathogenesis of atopic asthma, and that enhanced mediator release is due to a qualitative difference in signal transduction pathway between cross linking of receptors and calcium influx.

Basophils from different donors express a wide range of densities of cell surface IgE receptor (10^3 to 10^6 per basophil). Although serum total IgE concentration correlates with IgE receptor density (18) and allergen-induced basophil histamine release is dependent upon cell-surface IgE, maximal anti-IgE induced basophil histamine release reflects mediator releasability per se (19, 20). In the study about relation to serum IgE and anti-IgE-induced histamine release, Conroy et al. showed that cells from nonatopic donors were as sensitive as cells from atopic donors (3). Mita et al. also proved that anti-IgE-induced maximal basophil histamine releasability is independent upon the receptor density (20). They measured anti-mouse IgE-induced maximal BaHR after passive sensitization of basophils with mouse IgE to eliminate the effects of IgE concentration, and demonstrated that it was well correlated with anti-human IgE-induced maximal BaHR ($r=0.996$, $p=0.0023$). In this study, our aim was to compare mediator releasability in atopic and nonatopic asthmatics, two groups which were different in total IgE concentration. Because it had been shown to be unaffected by IgE receptor density, we therefore used anti-IgE (not allergen)-induced maximal histamine releasability as an index of IgE-mediated releasability per se.

Our results showed that anti-IgE induced maximal basophil histamine releasability correlated positively with the logarithmic value of total IgE concentration, indicating that atopy may influence mediator releasability via enhancing signal transduction. This finding contrasts with those of Conroy et al (3). The discrepancy can be explained by differences in mediator releasability indices used in the studies. Conroy adopted sensitivity as an index of mediator releasability, and this was expressed as the anti-IgE concentration needed to release 50% of total histamine released; we, on the other hand, chose maximal histamine releasability to represent reactivity of mediator releasability. These two indices have been shown to be independent variables (21).

A change in histamine releasability according to age is another possible explanation. In a basophil, this generally increases with age, although the biological significance of this phenomenon is not known (22). A previous study by Marone et al. reported a positive correlation between serum total IgE level and maximal histamine releasability in subjects less than 20 years of age, though among 63 healthy adults there was no relationship between the releasability and the IgE level (23). In this study, subjects were aged between four and 18 years, and so our results are consistent with those by Marone et al. (22). We suggest that the factors affecting IgE receptor-mediated histamine release differ according to age. In the younger group, aged less than 20, the amount of signal of IgE-receptor coupling or atopy itself may be a major factor in determining mediator release from basophils, but the effects of this signal or of atopy appear to diminish with age.

This study indicates that by enhancing mediator releasability as well as increasing IgE production to allergen, atopy plays an important role in the pathogenesis of bronchial asthma, enhanced anti-IgE-induced maximal histamine releasability in atopic asthmatics may be due to in vivo priming effects. Basophils pre-treated with various stimuli show increased mediator releasability; it has been reported that basophil histamine releasability was enhanced after priming with GM-CSF (24) and IL-3 (25), and the effects of IL-4 and IL-5 have been reported to be similar (26-28). In atopic patients, the profiles of cytokines excreted from lymphocytes are different to those in nonatopics, and this difference could influence the in vivo priming of basophils, leading to different mediator releasability. So far, evidence for priming responses in vivo is lacking but may be related to observations regarding releasability. To confirm the effects of in vivo

priming on basophil histamine releasability, further detailed studies are required.

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