Basophil histamine release by anti-IgE in subjects of chronic bronchitis and bronchial asthma

Yoshiro Tanizaki, Michiyasu Sudo, Hikaru Kitani, Hiroyuki Araki, Mitsuaki Tsuji, Kiyoshi Takahashi,* and Ikuro Kimura*

Division of Medicine, Misasa Hospital, Okayama University Medical School,
*2nd Department of Medicine, Okayama University Medical School.

Abstract: Histamine release from basophils induced by anti-IgE was studied in 8 patients with chronic bronchitis and 50 patients with bronchial asthma by analyzing doseresponse curves. As the result, there were no significant differences in maximum percent histamine release from basophils among three groups of healthy subjects (24.7±14.2%), patients with chronic bronchitis (27.7±22.1%) and those with bronchial asthma (28.4±17.0%). In the patients with bronchial asthma, the maximum percent histamine release was higher in accordance with higher serum IgE levels, and low maximum percent release was observed in patients with intrinsic asthma (14.1±7.2%).

Study of dose-response curves of anti-IgE-induced histamine release showed that a negative slope from E2 to E1 was observed in both healthy subjects and patients with chronic bronchitis. The majority of asthmatics with serum IgE levels of 501IU/ml or over showed a positive slope from E2 to E1.

Key words: Basophil response—Anti-IgE—Histamine release—chronic bronchitis—bronchial asthma

Introduction

The mechanism of histamine release induced by non-IgE-mediated stimuli (comp. 48/80¹, Ca ionophore A23187²) is different from that caused by antigen³–⁵, anti-IgE⁶, which are IgE-mediated stimuli. Histamine release from basophils mediated by IgE is induced by bridging of IgE molecules on the cells by these stimulating agents such as antigen and anti-IgE⁷,⁸. It is considered that mechanisms of histamine release from basophils by these agents are almost similar. However, a recent study has indicated that there are some differences in histamine release from basophils by antigen and anti-IgE⁹.

Majority of studies on histamine release from basophils has been performed using washed leukocytes. While, there are only a few reports about the release of histamine from whole blood¹⁰–¹³. In the present study, basophil response to anti-IgE in chronic bronchitis and bronchial asthma was examined by measuring the release of histamine from whole blood.
Subjects and Methods

Eight patients with chronic bronchitis (4 females and 4 males, age 50–72 years) and 50 patients with bronchial asthma (34 females and 16 males, age 16–71 years) were selected for the study of histamine release. The healthy individuals were examined as controls. The mean of serum IgE levels was 221 ± 63 IU/ml in the cases with chronic bronchitis, 463 ± 67 IU/ml in the cases with bronchial asthma and 147 ± 17 IU/ml in healthy controls.

Histamine release from basophils. It was carried out by the whole blood method as previously described\(^{12,13}\). Four ml of heparinized venous blood was drawn into a siliconed test tube and 0.2ml of various concentrations (10\(^{1}\)–10\(^{5}\) times dilution) of anti-IgE (Hoechst) was added. The mixture was incubated at 37°C for 15 minutes. The results were expressed as a percentage of the total blood content of histamine.

Analysis of dose-response curve. Examinations were made from two viewpoints, i.e. height of dose-response curve and gradient of curve between two points. The height of dose-response curve was expressed as the maximum percent histamine release (reactivity) induced by anti-IgE. Since it was only with 100-fold and 10-fold dilutions of anti-IgE that significant release of histamine was observed in the majority of cases, expression with a positive or negative slope from 100-fold dilution (E\(_2\)) to 10-fold dilution (E\(_1\)) of anti-IgE was used in analysis of dose-response curves (Fig. 1).

Determination of histamine was made using an automated histamine analysis system\(^{14,15}\) of Technicon. As a rule, administration of any drug was stopped within 12 hours prior to blood collection for the study.

Fig. 1. A schema of dose-response curve of anti-IgE-induced histamine release.
R, R'; basophil reactivity

Results

Maximum percent histamine release (reactivity) from basophils following addition of anti-IgE averaged 24.7 ± 14.2% (mean ± SD) (range:2.9–50.0%) in healthy subjects, 27.7 ± 22.1% (3.5–61.4%) in the subjects with chronic bronchitis and 28.4 ± 17.0% (2.7–69.4%) in the subjects with bronchial asthma. There were no significant differences in basophil reactivity among three groups. The results revealed that basophils from healthy subjects and patients with chronic bronchitis release significant amount of histamine when the cells were stimulated by anti-IgE. Among the cases with bronchial asthma, the patients with intrinsic asthma whose skin reaction to allergens is always negative showed a tendency to low maximum percent histamine release with a mean of 14.1 ± 7.2% (Fig. 2).

In the patients with bronchial asthma, maximum percent histamine release by anti-IgE was compared according to serum IgE levels. In the cases with serum IgE levels of 0–100 IU/ml, the maximum percent release averaged 17.1 ± 4.4% : with 101–200 IU/ml, 16.1 ± 3.5% : with 201–300 IU/ml, 20.2 ±
Basophil histamine release in chronic bronchitis and bronchial asthma

Fig. 2. Maximum percent histamine release (reactivity) in healthy controls, subjects with chronic bronchitis and bronchial asthma. (O: intrinsic asthma) *Mean±SD

3.3% with 301-500IU/ml, 29.6±4.4% with 501-1000IU/ml, 45.8±7.1% and with the level over 1001IU/ml, it was 47.8±5.7%. Thus, the maximum percent release was higher in accordance with higher serum IgE levels. Especially when serum IgE levels were over than 300IU/ml, maximum percent histamine release of 20% or over was induced in all of the cases, and the difference was significantly great compared with the cases with serum IgE levels of 300IU/ml or below (p<0.05). Among the latter cases, however, there were considerable number of cases in which maximum percent release exceed 20%.

Dose-response slopes from 100-fold (E2) to 10-fold (E1) dilution of anti-IgE were studied. As the result, a negative slope from E2 to E1 was observed in both healthy subjects and patients with chronic bronchitis. In these cases, maximum percent histamine release was induced by the low concentration of anti-IgE (E2) and the release of histamine was suppressed by the high concentration of anti-IgE (E1) (Fig. 3).

The majority of asthmatics with serum IgE levels of 500IU/ml or below showed a negative slope from E2 to E1, and maximum percent release was induced by the low concentration of 100-fold dilution (E2) in these cases like healthy subjects and patients with chronic bronchitis. On the other hand, the majority of the cases with levels of 501IU/ml or over showed a positive slope. Thus, it became clear that dose-response slopes from E2 to E1 of histamine release induced by anti-IgE would be negative in the cases with low serum IgE levels and positive in those with high serum IgE levels. The result suggests that basophils from the cases with high serum IgE levels require high concentrations of anti-IgE to cause maximum histamine release (Fig. 4).

Discussion

IgE-mediated histamine release from basophils is induced by stimuli such as antigen 3) -5) and anti-IgE 6). Histamine release
induced by these agents have generally been studied using washed leucocytes. From the viewpoint of clinical application, simple whole blood method seems to be more useful. Siraganian et al.\(^1\) compared washed leucocyte method with whole blood method, and suggested that the results of histamine release by these methods nearly agreed with each other. In a study of histamine release using whole blood, however, it is necessary to consider interaction between various factors contained in serum and stimulating agents.\(^2\) In the cases of histamine release induced by anti-IgE, it is IgE that comes into question among factors contained in serum.

In the present study, anti-IgE-mediated histamine release from basophils was investigated by analyzing dose-response curves. Lichtenstein, et al.\(^3\) observed histamine release from washed leucocytes regarding two aspects of reactivity and sensitivity of basophils. In their studies, basophil reactivity was expressed as maximum percent histamine release, and sensitivity as concentration of stimulating agents that induced 50\% or 30\% histamine release (HR\(_{50}\), HR\(_{30}\)). Using the present whole blood method, it was possible to observe reactivity indicated by maximum percent histamine release in the same way as washed leucocyte method. However, basophil sensitivity indicated by HR\(_{50}\) or HR\(_{30}\) could not be observed by the present method. The first reason is that since we used commercial anti-IgE serum, maximum percent histamine release was induced only by 10-fold and 100-fold dilutions of the anti-serum in any cases, and differences by various concentrations of anti-IgE were not observed well. Secondly, whole blood method did not yield high maximum percent release as with washed leucocyte method, and there were many cases in which even HR\(_{30}\) of Lichtenstein et al.\(^3\) was not achieved. Therefore, in the present study by whole blood method, dose-response slopes from 100-fold (E\(_2\)) to 10-fold (E\(_1\)) dilution of anti-IgE were used instead of basophil sensitivity indicated by HR\(_{50}\) or HR\(_{30}\). As the result, there was a general tendency for dose-response slopes from E\(_2\) to E\(_1\) to show negative gradient in the cases with low serum IgE levels and positive gradient in those with high serum IgE levels. This indicates that anti-IgE concentration required to induce maximum percent histamine release is lower in the cases with low serum IgE compared to those with high serum IgE levels. That is, basophils of the cases with low serum IgE levels appear to be able to react to lower concentration of anti-IgE. This is presumably due to interaction.

Fig. 4. Comparison between E\(_2\)- and E\(_1\)-induced histamine release in asthmatic subjects classified by serum IgE. E\(_2\) : x 10\(^2\) dilution, E\(_1\) : x 10 dilution of anti-IgE.
between IgE in serum and anti-IgE added. In the cases with high serum IgE levels, it seems that a larger amount of anti-IgE is required to induce maximum percent histamine release because of interaction between much IgE in serum and anti-IgE. The results obtained in the present study show that observation of basophil sensitivity by washed leucocyte method is not possible by whole blood method for the interaction of IgE in serum. However, regarding basophil reactivity, similar tendency was observed by both washed leucocyte method and whole blood method.

There was no significant differences in maximum percent histamine release from basophils induced by anti-IgE among three groups of healthy subjects, patients with chronic bronchitis and those with bronchial asthma. In the cases of bronchial asthma, maximum percent histamine release was related to some extent with serum IgE levels, but there were some cases with low serum IgE levels who showed high values of maximum percent release. On the other hand, maximum percent release was always low in the cases with intrinsic asthma, who had no participation of IgE in the onset mechanism of the disease. Based on these results, it is considered that observation of anti-IgE-induced histamine release from basophils can be used as an important index to know whether IgE-mediated reaction is involved in occurrence of bronchial asthma.

References