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Abstract

Candida albicans-induced histamine release from basophils was studied in 54 patients with bronchial asthma in comparison with the release caused by house dust and anti-IgE. The release of histamine induced by C. albicans and that induced by house dust were closely related to the serum levels of specific IgE antibodies as expressed by RAST scores. A correlation of C. albicans-induced histamine release with the release caused by anti-IgE was not generally observed. On the other hand, a close correlation was found between house dust- and anti-IgE-induced histamine release. It was suggested from these results that the differences between C. albicans- and house dust-induced histamine release might be due to the different antigenicity of the two allergens.

KEYWORDS: histamine release, C. albicans, house dust, anti-IgE, antigeniciy

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CANDIDA-INDUCED HISTAMINE RELEASE FROM BASOPHILS: RELATIONSHIP TO HOUSE DUST- AND ANTI-IgE-INDUCED SECRETION

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Abstract. *Candida albicans*-induced histamine release from basophils was studied in 54 patients with bronchial asthma in comparison with the release caused by house dust and anti-IgE. The release of histamine induced by *C. albicans* and that induced by house dust were closely related to the serum levels of specific IgE antibodies as expressed by RAST scores. A correlation of *C. albicans*-induced histamine release with the release caused by anti-IgE was not generally observed. On the other hand, a close correlation was found between house dust- and anti-IgE-induced histamine release. It was suggested from these results that the differences between *C. albicans*- and house dust-induced histamine release might be due to the different antigenicity of the two allergens.

Key words : histamine release, *C. albicans*, house dust, anti-IgE, antigeniciy.

It is thought that *Candida albicans* is one of the main allergens causing bronchial asthma (1). *C. albicans*-induced allergic reactions in bronchial asthma are somewhat more complicated than those induced by house dust. Increased production of precipitating antibodies which participate in Arthus type (type Ⅲ) allergic reactions is observed when patients with bronchial asthma are sensitized with *C. albicans* (2). At the same time, the allergen stimulates production in asthmatic patients of specific IgE antibodies, which participate in immediate (type I) allergic reactions (3, 4). Bronchial challenge tests with *C. albicans* cause immediate and late asthmatic responses with a high incidence. These findings suggest that the antigenicity of *C. albicans* is different from that of house dust. There being no available information about the release of histamine from basophils induced by *C. albicans*, *C. albicans*-induced histamine release was compared with the release caused by house dust and anti-IgE.

SUBJECTS AND METHODS

Subjects. Fifty-four patients with bronchial asthma (36 females and 18 males) were selected for this study. Histamine release from basophils induced by *C. albicans* and anti-IgE was

examined in 32 patients, ranging in age from 21 to 72 years (mean, 49.3 years), whose skin reaction to *C. albicans* was positive. The release of histamine induced by house dust and anti-IgE was examined in 32 patients, ranging in age from 16 to 70 years (mean, 41.9 years), with a positive skin reaction to house dust.

Histamine release. Histamine release from basophils was induced by a whole blood method, as previously described (5-8). To 4 ml of whole blood was added 0.2 ml of various concentrations of *C. albicans*, house dust and anti-IgE, and the mixture was incubated at 37 ℃ for 15 min. After the incubation, histamine content of the cells and supernatant fluid was measured by an automated fluorometric histamine analysis system (Technicon) (9). The results were expressed as a percentage of the total histamine content.

Dose-response curves of histamine release. The dose-response of histamine release was examined by addition of three different dilution, $\times 10^4$, $\times 10^3$ and 10^2, of house dust, *C. albicans* (Torii Co.) or anti-IgE. The results were compared in relation to the RAST scores to each allergen.

Serum IgE and specific IgE. Total serum IgE levels were measured by a radioimmunosorbent test (RIST). Specific IgE antibodies for *C. albicans* and house dust were estimated by the radioallergosorbent test (RAST).

RESULTS

Dose-response curves of house dust- and C. albicans-induced histamine release. House dust caused a significant amount of histamine release from basophils of asthmatic patients with a RAST score of 2 + or higher in a dose-dependent fashion. On the other hand, the percent histamine release in cases with a RAST score of 1 + or 0 + was very low at any concentration of house dust extract. A statistically significant difference was found in the histamine release induced by the highest concentration (H_1) of house dust between cases with a RAST score of 2 + and those with a RAST score of 1 + ($p<0.01$).

C. albicans also induced histamine release from basophils of asthmatic subjects sensitive to the allergen (RAST score: 2 + or higher). The amount of histamine release induced by *C. albicans* was very low in cases with a RAST score of 1 + or 0 +. A significant difference was present in histamine release elicited by the three concentrations of *C. albicans* between cases with a RAST score of 2 + and those with a score of 1 + (10^2: $P<0.001$, 10^3, 10^4: $p<0.01$) (Fig. 1).

Serum IgE levels and histamine release induced by house dust and anti-IgE. House dust- and anti-IgE-induced histamine release was compared in subjects classified by serum IgE levels. The number of cases showing a positive RAST score to house dust tended to increase as serum IgE levels were higher, so that the release of histamine by house dust was higher with higher serum IgE levels. The house dust-induced release of histamine in cases with positive RAST scores was high regardless of the serum IgE level. Anti-IgE-induced histamine release was higher with higher serum IgE levels. A significant difference was found in histamine release between cases with low (0-200 IU/ml) and those with high (more than 1001 IU/ml) serum IgE levels ($p<0.01$) (Table 1).

Serum IgE levels and histamine release induced by C. albicans and Anti-IgE. C. albicans-

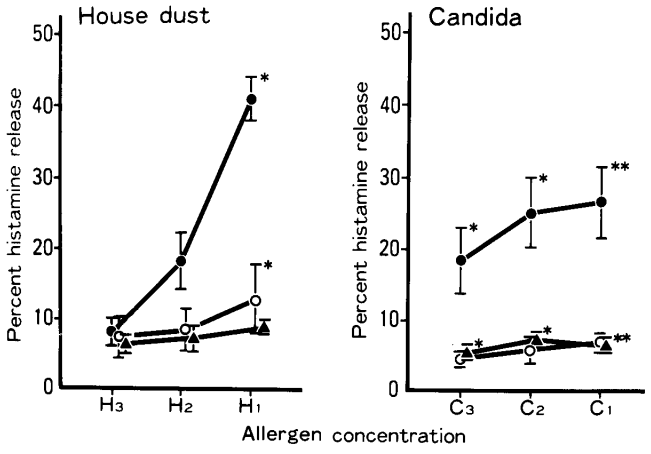

Fig. 1. Dose-response curves of house dust- and *C. albicans*-induced histamine release in cases with a RAST score of 2+ or higher (house dust: N = 15, *Candida*: N = 12) (●——●), 1+ (house dust: N = 3, *Candida*: N = 3) (○——○), and 0+ (house dust: N = 5, *Candida*: N = 17) (▲——▲) to the corresponding allergen. Three different dilutions, $\times 10^4$ (H_3, C_3), $\times 10^3$ (H_2, C_2) and $\times 10^2$ (H_1, C_1), of house dust or *C. albicans* were used. *P<0.01, **p<0.001.

TABLE 1. SERUM IgE LEVELS AND HISTAMINE RELEASE INDUCED BY HOUSE DUST AND ANTI-IgE

Serum IgE (IU/ml)	Positive RAST to HD	% Histamine release induced by HD: Total cases	HD: Cases with positive RAST	Anti-IgE: Total cases	Anti-IgE: Cases with positive RAST
0-200	2/5[a] (40 %)	25.7[b] ±9.3	46.9 ±8.1	19.5* ±6.5	31.9 ±11.1
201-300	2/4 (50 %)	31.2 ±9.9	39.2 ±7.7	30.3 ±4.1	34.2 ± 2.3
301-500	4/5 (80 %)	32.9 ±8.3	40.3 ±4.9	31.1 ±5.4	32.7 ± 6.6
501-1000	7/9(77.8 %)	32.6 ±6.3	39.1 ±5.9	34.0 ±6.3	42.3 ± 4.1
1000<	9/9(100 %)	38.7 ±3.6	38.7 ±3.6	47.2* ±5.0	47.2 ± 5.0

[a] No of cases with a positive RAST score (more than 2+)/total number
[b] mean ± SEM, *p<0.01. HD, house dust.

and anti-IgE-induced histamine release was compared in subjects whose skin reaction to *C. albicans* was positive. The incidence of cases with a positive RAST score to *C. albicans* did not increase as serum IgE levels were higher, and the release of histamine induced by *C. albicans* did not correlate with serum IgE levels. The release induced by anti-IgE correlated to a certain extent with serum IgE levels. A significant difference was found in anti-IgE-induced histamine release

TABLE 2. SERUM IgE LEVELS AND HISTAMINE RELEASE INDUCED BY *C.ALBICANS* AND ANTI-IgE

Serum IgE (IU/ml)	Positive RAST to C.a.	% Histamine release induced by *C.albicans* Total cases	*C.albicans* Cases with positive RAST	Anti-IgE Total cases	Anti-IgE Cases with positive RAST
0-200	4/9[a](44.4%)	13.5[b] ±4.8	15.8[c] ±7.6	15.5* ±3.8	13.8 ±5.8
201-300	1/5 (20%)	9.3 ±2.7	8.4	20.8 ±7.1	11.1
301-500	2/5 (40%)	13.7 ±4.5	24.4 ±3.3	29.6 ±6.0	27.1 ±2.3
501-1000	4/10(40%)	20.2 ±6.6	41.2[c] ±8.6	31.1 ±6.3	25.7 ±7.3
1000<	1/3 (33.3%)	14.4 ±11.7	37.8	49.0* ±9.2	67.4

[a] No of cases with a positive RAST score (more than 2+)/total number.
[b] mean ± SEM, [c] not significant, * $p<0.01$. C.a. *Candida.*

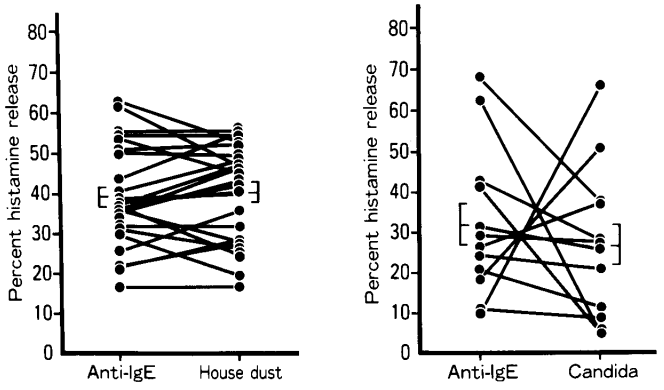

Fig. 2. Correlation between house dust- and anti-IgE-induced histamine release, and between *C.albicans*- and anti-IgE-induced release in cases with RAST scores of 2+ or higher. Vertical bars represent the mean ± SEM.

between cases with low (0-200 IU/ml) and those with high (more than 1001 IU/ml) serum IgE levels ($p<0.01$) (Table 2).

Correlation among house dust-, C.albicans- and anti-IgE-induced histamine release. The mean maximum percent histamine release induced by house dust was 40.3 ± 2.4% in cases with a RAST score of 2+ or higher. The release induced by anti-IgE (39.1 ± 2.6 %) was similar to that induced by house dust. As shown in Fig. 2, basophils from the same subject released histamine to almost the same degree whether incubated with house dust or anti-IgE (coefficient of correlation; $r=0.52$, $p<0.02$). In cases showing a positive RAST score to *C.albicans*, the mean percent

histamine release caused by *C.albicans* or anti-IgE was 27.4 ± 5.4 % and 32.3 ± 5.3 %, respectively. The average histamine release induced by the two stimulating agents appeared to be similar. However, the reactivity of basophils to *C.albicans* and anti-IgE was markedly different in individual patients, as shown in Fig. 2. Basophils from one case released a large amount of histamine (66.0 %) by stimulation with *C.albicans*, and little histamine (9.3 %) by anti-IgE stimulation. In another case, the percent release was 4.6 % by *C.albicans* and 63.0 % by anti-IgE. Fig. 2 also shows that *C.albicans* induces no significant amount of histamine release in some cases with positive RAST scores (Fig. 2).

DISCUSSION

C.albicans and house dust are among the main allergens causing bronchial asthma. Both allergens induce production of specific IgE antibodies in patients with bronchial asthma, but house dust induces production of specific IgE antibodies with a much higher incidence than *C.albicans* (3). In the present study, 24 cases (75.0 %) out of 32 cases with a positive skin reaction to house dust showed a RAST score of 2+ or higher. On the other hand, 12 (37.5 %) out of 32 cases sensitive to *C.albicans* had a RAST score of 2+ or higher. *C.albicans*, however, induces production of precipitating antibodies much more frequently than house dust allergen (2), and bronchial challenge with *C.albicans* frequently causes both immediate and late asthmatic responses. The production of precipitating antibodies and late asthmatic response suggest the presence of an Arthus (type III) type allergic reaction in *C.albicans*-induced asthma.

As mentioned above, it is thought that precipitating antibodies- (type III) and an IgE-mediated (type I) allergic reaction participate in *C.albicans*-induced bronchial asthma. Although the presence of an IgE-mediated reaction in *C.albicans*-induced asthma has been suggested by several authors (2-4), histamine release from basophils of asthmatic subjects induced by *C.albicans* has not been examined. In this study, *C.albicans*-induced release of histamine from basophils was examined in patients with bronchial asthma whose skin reaction to the allergen was positive. The results demonstrated that *C.albicans* as well as house dust induces histamine release in a dose-dependent manner, and that the release by the two allergens is mediated by specific IgE antibodies. In this study, the difference in IgE-mediated histamine release among house dust, *C. albicans* and anti-IgE also was examined. The amount of histamine release induced by house dust paralleled the amount of release elicited by anti-IgE. The result shows that basophil reactivity to house dust and anti-IgE is similar when the reaction is caused by an allergen-IgE interaction. On the other hand, the release of histamine induced by *C.albicans* was very different from that induced by anti-IgE. The difference between *C.albicans*- and house dust-induced histamine release might be due to the different antigenicity of the

two allergens, as indicated by the following observation. House dust tends to sensitize young patients under 20 years of age, while *C.albicans* sensitization is most frequently observed in patients over 40 (10). Basophil reactivity as expressed by histamine release decreases in patients over 40 in spite of high serum IgE levels (data not shown). Cases with a high serum IgE level are easily sensitized by house dust, while the incidence of cases sensitive to *C.albicans* does not correlate with serum IgE levels. *C.albicans*-induced histamine release is generally less than house dust-induced release, as shown in Tables 1 and 2. Furthermore, *C.albicans*-induced release of histamine correlates to a certain extent with the RAST scores, but not always, as does house dust-induced release. Sometimes histamine release is not elicited even in cases with positive RAST scores, and sometimes a significant amount of histamine release is caused in cases with negative RAST scores (11). These phenomena might explain the difference between house dust- and *C.albicans*-induced histamine release. Whether or not other mechanisms may result in the difference between house dust- and *C.albicans*-induced release remains to be investigated.

REFERENCES

1. Itkin, I.H. and Dennis, M.: Bronchial hypersensitivity to extract of Candida albicans. *J. Allergy* **37**, 187-194, 1966.
2. Pepys, J., Faux, J.A., Longbottom, J.L., McCarthy, D.S. and Hargreave, F.E.: Candida albicans precipitins in respiratory disease in man. *J. Allergy* **4**, 305-318, 1968.
3. Kurimoto, Y.: Relationship among skin tests, bronchial challenge and serology in house dust and Candida albicans allergic asthma. *Ann. Allergy* **35**, 131-141, 1975.
4. Edge, G. and Pepys, J.: Antibodies in different immunoglobulin classes to Candida albicans in allergic respiratory disease. *Clin. Allergy* **10**, 47-58, 1980.
5. Tanizaki, Y., Komagoe, H., Sudo, M., Morinaga, H., Kitani, H., Goda, Y., Tada, S., Takahashi, K. and Kimura, I.: IgE-mediated histamine release from whole blood in atopic asthmatics. *Jpn. J. Allergol.* **32**, 1079-1083, 1983.
6. Tanizaki, Y., Komagoe, H., Morinaga, H., Kitani, H., Goda, Y. and Kimura, I.: Allergen- and anti-IgE-induced histamine release from whole blood. *Int. Arch. Allergy Appl. Immunol.* **73**, 141-143, 1984.
7. Tanizaki, Y., Komagoe, H., Sudo, M., Morinaga, H., Kitani, H., Tada, S., Takahashi, K. and Kimura, I.: Histamine release from whole blood induced by anti-IgE: Relationship to patient age, age at onset and serum IgE levels. *Acta Med. Okayama* **38**, 275-280, 1984.
8. Tanizaki, Y., Komagoe, H., Sudo, M., Morinaga, H., Kitani, H., Nakagawa, S., Takahashi, K. and Kimura, I.: Reactivity of sensitized basophils, as expressed by histamine release. *Jpn. J. Allergol.* **33**, 31-35, 1984.
9. Siraganian, R.P.: An automated continuous-flow system for the extraction and fluorometric analysis of histamine. *Anal. Biochem.* **57**, 383-394, 1974.
10. Tanizaki, Y., Komagoe, H., Sudo, M., Kitani, H., Nakagawa, S., Nakayama, K., Tada, S., Takahashi, K. and Kimura, I.: Characteristics of Candida allergen in bronchial asthma.

Jpn. Soc. Chest Dis. (in Japanese) (in press).

11. Tanizaki, K., Komagoe, H., Sudo, M., Kitani, H., Nakagawa, S., Tada, S., Takahashi, K. and Kimura, I.: Basophil histamine release induced by Candida albicans. Relation to specific IgE and IgG antibodies. *Jpn. J. Allergol.* (in press).