

Investigation of the mechanism of alcohol-induced bronchial asthma

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Background: Many Japanese patients with asthma experience episodes or exacerbation of asthma after alcohol consumption. This phenomenon is not seen in Caucasians and is specific to Asians. This has been thought to be attributable to a difference in alcohol metabolism, in particular the metabolism of acetaldehyde, between Asians and Caucasians.

Methods: An oral ethanol challenge test, a leukocyte histamine release test, and an ELISA for detection of IgE specific to acetaldehyde-human serum albumin conjugate were carried out in 42 adults with bronchial asthma and nine healthy adults.

Results: Fifty-five percent of the patients with asthma responded to the ethanol challenge and showed a 20% or greater reduction in forced expiratory volume in 1 second. Blood acetaldehyde and plasma histamine levels were significantly higher in responders than in nonresponders. The leukocyte histamine release test revealed no ethanol-induced histamine release. Acetaldehyde, on the other hand, was found to induce histamine release in a volume-dependent manner. The histamine release was significantly higher in the asthma group (both responders and nonresponders) than in the healthy control group. ELISA did not detect any IgE specific to acetaldehyde-human serum albumin conjugate.

Conclusion: Alcohol-induced bronchial asthma seems to develop as follows. Alcohol elevates blood acetaldehyde levels, which leads to degranulation of mast cells (or basophils). The resultant release of chemical mediators, such as histamine, induces asthma. (*J ALLERGY CLIN IMMUNOL* 1996;97:74-84.)

Key words: Bronchial asthma, alcohol, Asians, Caucasians, histamine release, acetaldehyde

Japanese patients with bronchial asthma often experience asthma attacks or airway constriction after alcohol consumption. We called this phenomenon "alcohol-induced bronchial asthma." This phenomenon is absent in Caucasians and is specific to Asians. The incidence of this phenomenon thus differs among races.¹ In our previous questionnaire survey of 102 Japanese patients with asthma, 68 (67%) responded that they had experienced exacerbation of their asthma after alcohol consumption. Thus about half of the Japanese patients with

Abbreviations used

ALDH:	Aldehyde dehydrogenase
DSCG:	Disodium cromoglycate
FBS:	Fetal bovine serum
FEV ₁ :	Forced expiratory volume in 1 second
HSA:	Human serum albumin
PBS:	Phosphate-buffered saline

asthma had experienced this phenomenon. In Asians with asthma, any type of alcohol-containing beverage can bring on an asthma attack, and oral administration of pure ethanol also induces asthma.^{1,2} In Caucasians with asthma, oral administration of pure ethanol did not induce asthma, and their asthma attacks after alcohol consumption have been attributed to their hypersensitive responses to some additives contained in alcoholic beverages.³ Thus alcohol consumption seems to serve as an important factor responsible for induc-

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tion of asthma attacks in Asian populations. The incidence of uncomfortable symptoms (e.g., facial hot flushes, palpitations, and vomiting) induced by alcohol consumption is also reported to be higher in Asians than in Caucasians, suggesting a race-related difference in the metabolism of and responses to ethanol.⁴⁻¹³

However, few studies have been carried out regarding the mechanism of alcohol-induced asthma, and there has been no study concerning race-related differences in this phenomenon. This study was undertaken to examine the incidence and mechanism of alcohol-induced bronchial asthma specific to Asians.

METHODS

Subjects

The subjects were 42 adults with bronchial asthma (22 men and 20 women), with ages ranging from 22 to 65 years (mean, 38.1 years). Asthma was mild in 32 patients and moderate in 10. The asthma type was atopic in 26 patients and nonatopic in 16. The severity and the type of asthma were classified according to the criteria proposed by the Evaluation Committee of Severity of Bronchial Asthma, Japanese Society of Allergology.¹⁴ All tests were carried out when the subjects were free of asthma attacks. The use of bronchodilators was suspended for more than 24 hours before the tests. The use of steroids, antiallergy agents, and antihistamines was avoided for more than 48 hours before the tests.

Nine healthy adults served as normal control subjects.

Oral ethanol challenge

Pure ethanol, free of substances that may act as antigens, was dissolved in 5% glucose solution to yield a 10% ethanol solution. Patients with asthma and normal control subjects drank 300 ml of this solution (containing 30 gm of ethanol) in 5 to 10 minutes. All subjects gave informed consent to participate in this study, after they had received adequate information concerning the design and significance of the study and possible adverse reactions.

Pulmonary function measurement

With an autspirometer (Spiro Analyzer ST-200, Fukuda Denshi Co., Ltd., Tokyo, Japan), forced expiratory volume in 1 second (FEV₁) was measured immediately before and 15, 30, 60, and 120 minutes after ethanol challenge.

Blood sampling and measurement

Blood was drawn from the cubital vein immediately before and 15, 30, 60, and 120 minutes after ethanol challenge. Blood ethanol, acetaldehyde, and histamine levels were measured with the use of these samples. Heparinized whole blood (5 ml) was frozen for gas

chromatographic measurement of ethanol level. Heparinized whole blood (5 ml) was frozen for gas chromatographic measurement of acetaldehyde level. Plasma histamine level in 7 ml of blood, collected with an ethylenediaminetetraacetic acid-2 sodium-treated syringe, was measured, by radioimmunoassay.

Leukocyte histamine release test

Blood (400 ml), collected from the cubital vein, was combined with 0.4 ml of heparin (sodium heparin, 1 mg/ml). The heparinized blood was combined with 8 ml of 4.5% dextran solution. The mixture was agitated, and the test tube containing the mixture was then left standing upright for 30 minutes at room temperature to separate the plasma-leukocyte fraction from the erythrocyte fraction. The plasma-leukocyte fraction was transferred into another test tube and centrifuged at 250 g for 15 minutes to remove the plasma fraction. The leukocyte fraction, obtained in this way, was washed three times in Tyrode's buffer (NaCl, 137 mmol/L; KCl, 2.7 mmol/L; CaCl₂, 1.8 mmol/L; MgCl₂, 1.1 mmol/L; NaHCO₃, 11.9 mmol/L; NaH₂PO₄, 0.4 mmol/L; D-glucose, 5.6 mmol/L). It was then suspended in 5 ml of Tyrode's buffer.

The leukocyte suspension (450 μ l) was poured into a 4 ml plastic tube (Shionogi Tube; Shionogi & Co. Ltd., Osaka, Japan). The suspension was incubated at 37° C for 40 minutes in the presence of ethanol (2, 10, 20, or 100 mmol/L) or acetaldehyde (2, 10, 20, or 100 μ mol/L). Spontaneous histamine release and histamine contents in leukocytes were measured by pouring 50 μ l of Tyrode's buffer (instead of 450 μ l of leukocyte suspension) into another test tube and subsequently incubating this tube in a similar way. At the end of the incubation period, the tubes were ice-cooled and centrifuged at 250 $\times$ g and 4° C for 5 minutes. The supernatant was collected into another tube and stored frozen at -20° C until it was used for histamine measurement. The tube for measurement of histamine contents in leukocytes was subjected to 5 seconds of ultrasonic cell destruction before storage.

Histamine was quantified by radioimmunoassay. The histamine release rate was calculated with the following equation:

$$\%LHR = \{([H] - [S]) \div ([T] - [S])\} \times 100$$

where LHR denotes leukocyte histamine release, [T] denotes total histamine content in cells, [S] indicates the amount of spontaneously released histamine, and [H] is the amount of chemical-stimulated histamine release.

Measurement of IgE specific to acetaldehyde-human serum albumin conjugate

According to the method of Donohue et al.,¹⁵ we conjugated acetaldehyde to human serum albumin (HSA) for use as an antigen in detecting IgE specific to this conjugate in blood in an ELISA.

First, the acetaldehyde-HSA conjugate was dissolved

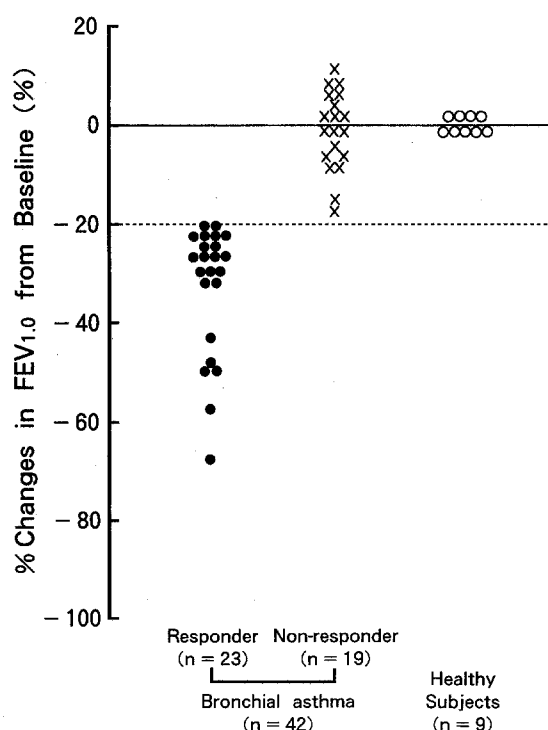


FIG. 1. Peak percent change in FEV₁ after ethanol challenge.

in 0.05 mol/L sodium carbonate buffer (pH 9.6) in a concentration of 200 μ g/ml. Each well of a microplate for ELISA (Nunc F Immunoplate, Inc., Copenhagen, Denmark) was coated with this solution (200 μ l/well) and left standing overnight at 4° C. After the plate was washed three times in phosphate-buffered saline (PBS)-Tween (pH 7.2), 100% fetal bovine serum (FBS) was poured into the plate (200 μ l/well) and incubated at room temperature for 2 hours to induce blocking. Subsequently, a serum sample from a patient or from a normal control subject, diluted 1:4 with 100% FBS, was poured into the plate (200 μ g/well), and the plate was left standing at room temperature for 2 hours. The plate was subsequently washed three times with PBS-Tween. Alkaline phosphatase-conjugated goat anti-human IgE antibody, dissolved 1:1000 with 50% FBS-PBS-Tween, was added to the plate (200 μ l/well). After the plate was left standing at room temperature for 2 hours, it was washed three times with PBS-Tween. p-Nitrophenyl phosphate, dissolved in 10% diethanolamine buffer solution (pH 9.8) in a concentration of 1 mg/ml, was then added to the plate (200 μ l/well). The plate was left standing at room temperature for 30 minutes and washed three times in PBS-Tween. The reaction was stopped by adding 1.5N NaOH to the plate (100 μ l/well). The absorbance of the sample at 410 nm was measured with an ELISA analyzer (MR600 Microplate Reader; Dynatech Corporation, Burlington, Mass.).

Sera with an absorbance more than double the absorbance in normal sera were rated as positive.

Inhibition by drugs

Patients who responded positively to the oral ethanol challenge test received the same test again more than 1 week later. Before the second oral ethanol challenge test, the patients were treated with one of three drugs: cyproheptadine hydrochloride, an antihistamine; disodium cromoglycate (DSCG), an agent that suppresses the release of chemical mediators; and atropine sulfate, an anticholinergic agent. The effects of these agents on the oral ethanol challenge were examined. The drug trials were done in random order.

Cyproheptadine. Eight milligrams of cyproheptadine was administered orally 40 minutes before the ethanol challenge.

DSCG. The subjects inhaled one ampule of DSCG (20 mg) with a Nissho-type jet nebulizer, 30 minutes before the ethanol challenge.

Atropine. The subjects inhaled 6 ampules of injectable atropine sulfate solution (0.5 mg/ampule, 3 mg in total) with a Nissho-type jet nebulizer, 20 minutes before the ethanol challenge.

Statistical analysis

The data were statistically tested with Student's *t* test. A *p* value of less than 0.05 was regarded as significant.

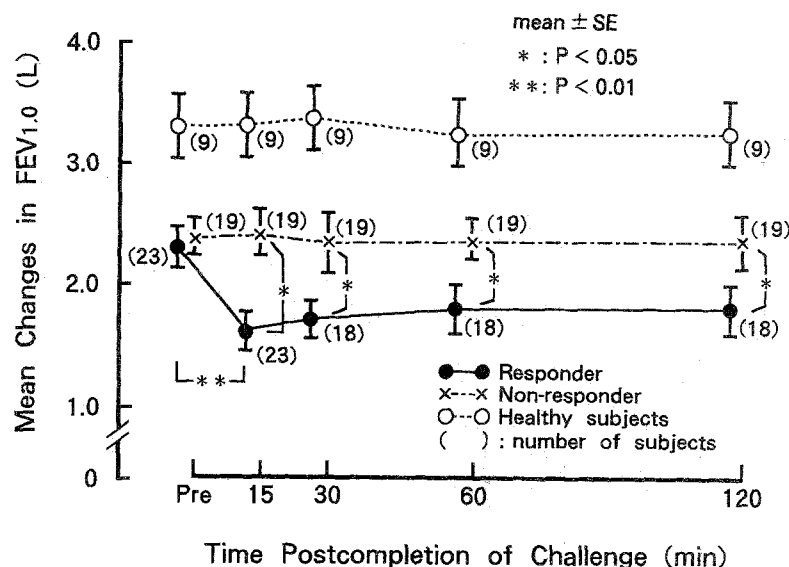


FIG. 2. Serial changes in FEV_1 after ingestion of ethanol.

RESULTS

Changes in pulmonary function

The percentage of change in FEV_1 was calculated with the following equation:

$$\text{Percent change in } FEV_1 = \{(\text{prechallenge level} - \text{postchallenge level}) \div \text{prechallenge level}\} \times 100$$

Patients in whom this value was greater than 20% were regarded as responders to the ethanol challenge. In this study, patients showing a 20% or more decrease in FEV_1 within 120 minutes after ethanol challenge were considered to be responders. In most patients, FEV_1 decreased by 20% or more within 15 to 30 minutes after challenge. Of the 42 patients with asthma, 23 (54.8%) were responders. These 23 patients were assigned to the responder group, and the remaining 19 patients were assigned to the nonresponder group. The percent change in FEV_1 in normal control subjects was 5% or smaller (Fig. 1).

Fig. 2 shows the time course of FEV_1 before and after the ethanol challenge. The prechallenge pulmonary function did not differ significantly between the responder group and the nonresponder group. The responder group showed a marked reduction in FEV_1 between 15 and 30 minutes after the ethanol challenge. Five of the 23 responders had intense dyspnea. These five patients inhaled salbutamol after their pulmonary function was measured 15 minutes after the ethanol chal-

lenge. The data from these five patients, collected 30 minutes after the ethanol challenge, were excluded from evaluation.

Blood ethanol level

In all three groups (normal control, responder, and nonresponder), blood ethanol levels reached a peak 15 to 30 minutes after the ethanol challenge and decreased thereafter, without showing any significant intergroup difference (Fig. 3).

Blood acetaldehyde level

After the ethanol challenge, blood acetaldehyde levels reached a peak between 15 and 30 minutes and decreased thereafter (Fig. 4). This parameter was significantly higher in responders than in nonresponders from the fifteenth to sixtieth minute after the ethanol challenge. The peak blood acetaldehyde level differed significantly ($p < 0.05$) between responders ($28.3 \pm 14.4 \mu\text{mol/L}$) and nonresponders ($15.2 \pm 7.3 \mu\text{mol/L}$). The blood acetaldehyde level in normal control subjects did not differ significantly from that in responders or nonresponders.

Plasma histamine level

The responder group showed a significant elevation in plasma histamine level after the ethanol challenge: values were $4.5 \pm 2.4 \text{ ng/ml}$ before the challenge, $14.5 \pm 7.6 \text{ ng/ml}$ 15 minutes after the challenge, $20.5 \pm 8.6 \text{ ng/ml}$ at 30 minutes, $24.3 \pm 7.4 \text{ ng/ml}$ at 60 minutes, and $27.4 \pm 8.5 \text{ ng/ml}$ at

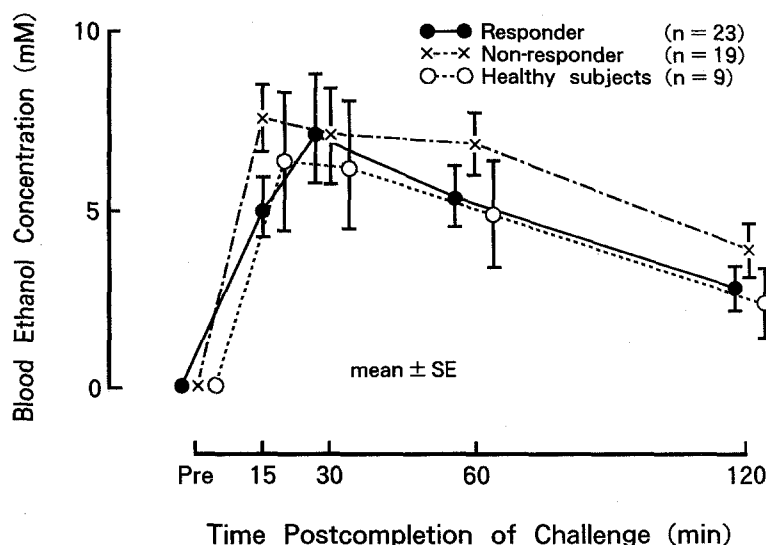


FIG. 3. Mean change in blood ethanol concentration after ingestion of ethanol.

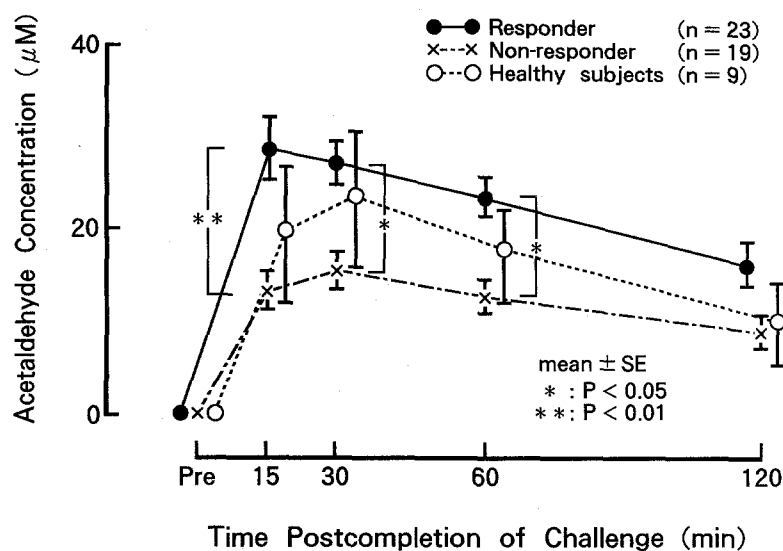


FIG. 4. Mean change in blood acetaldehyde concentration after ingestion of ethanol.

120 minutes. The nonresponder group and the normal control group showed no significant change in plasma histamine levels after the ethanol challenge (Fig. 5). The plasma histamine levels at 15, 30, 60, and 120 minutes were significantly higher in the responders than in the nonresponders and normal control subjects.

Leukocyte histamine release

It is known that blood ethanol level rises to about 10 to 20 mmol/L after consumption of ordinary amounts of alcohol. In this study, we examined leukocyte histamine release in a blood ethanol concentration range up to 100 mmol/L.

Ethanol in this range did not induce leukocyte histamine release in any of the three groups (responders, nonresponders, or normal control), as shown in Fig. 6.

Percentage of histamine release caused by acetaldehyde

The peak blood level of acetaldehyde after the oral ethanol challenge ranged from 7.4 to 67.5 $\mu\text{mol/L}$ in individual subjects. On the basis of this result, we examined percent histamine release at four blood acetaldehyde levels (2, 10, 20, and 100 $\mu\text{mol/L}$). This analysis showed that histamine release was dependent on acetaldehyde levels in all

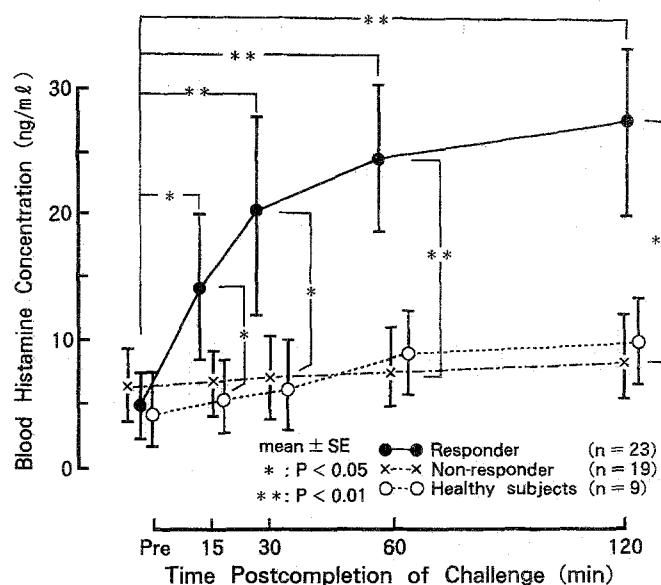


FIG. 5. Mean change in blood histamine concentration after ingestion of ethanol.

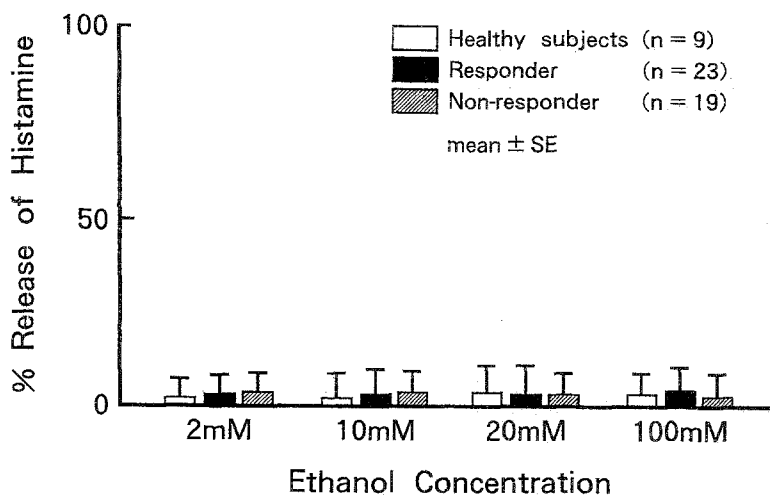


FIG. 6. Leukocyte histamine release induced by ethanol (2, 10, 20, and 100 mmol/L).

groups. When percent histamine release at each acetaldehyde level was compared among the three groups, histamine release was significantly enhanced in both responder and nonresponder groups of patients with asthma when compared with normal control subjects. This parameter, however, did not differ significantly between the responder and nonresponder groups of patients with asthma (Fig. 7).

IgE specific to acetaldehyde-HSA conjugate

IgE specific to acetaldehyde-HSA conjugate, as assessed by ELISA, was negative in all patients with asthma. The optical density value did not

differ significantly between patients with asthma and normal control subjects (Fig. 8).

Inhibition by drugs

Inhibitory action of oral cyproheptadine (Fig. 9, A). FEV₁ before oral treatment with 8 mg of cyproheptadine did not differ significantly from FEV₁ measured 40 minutes after treatment (i.e., immediately before ethanol challenge). FEV₁ values 60 and 120 minutes after ethanol challenge were 1.65 ± 0.30 L and 1.73 ± 0.32 L in the nonpretreatment group and 2.15 ± 0.23 L and 2.25 ± 0.20 L in the cyproheptadine-pretreated group, respectively. Thus pretreatment with cyprohepta-

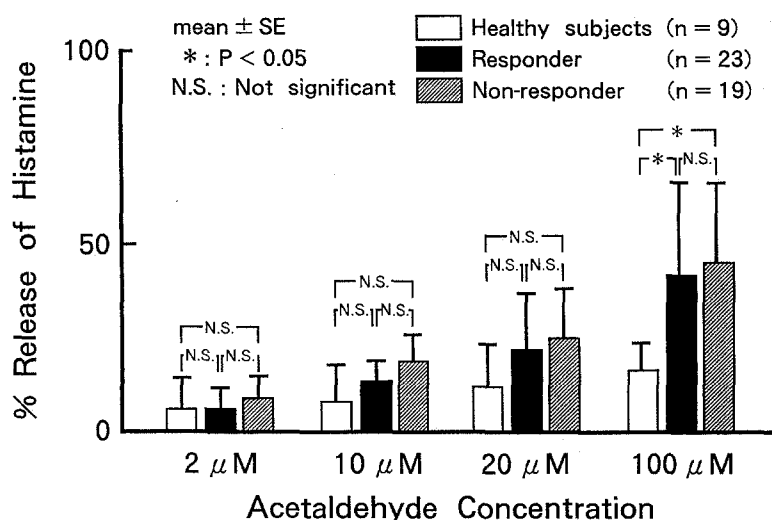


FIG. 7. Leukocyte histamine release induced by acetaldehyde (2, 10, 20, and 100 μ mol/L).

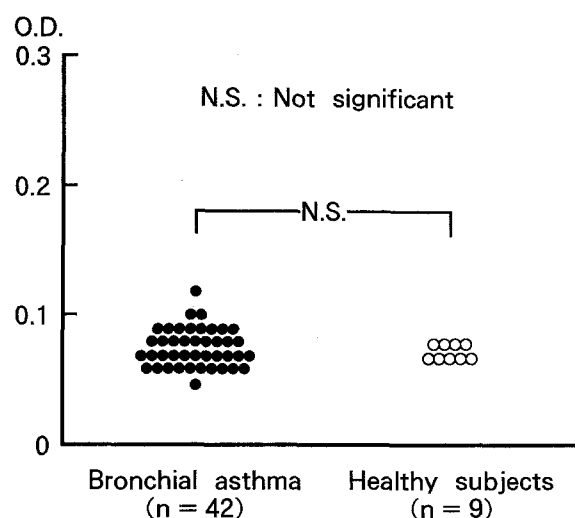


FIG. 8. IgE antibodies specific for acetaldehyde-HSA. O.D., Optical density.

dine significantly suppressed the ethanol-induced reduction in FEV_1 ($p < 0.05$).

Inhibition by DSCG inhalation (Fig. 9, B). Inhalation of 20 mg of DSCG did not affect the FEV_1 measured 30 minutes after inhalation (i.e., immediately before the ethanol challenge). FEV_1 at 15 and 30 minutes after ethanol challenge was 1.45 ± 0.24 L and 1.57 ± 0.22 L in the nonpretreatment group and 2.02 ± 0.25 L and 2.04 ± 0.21 L in the DSCG pretreatment group. Thus DSCG inhalation before ethanol challenge significantly suppressed the ethanol-induced reduction in FEV_1 at 15 and 30 minutes ($p < 0.05$), although no such effect was observed at 60 and 120 minutes.

Inhibition by atropine inhalation (Fig. 9, C). Atropine inhalation also had no effect on FEV_1 before ethanol challenge. After ethanol challenge, FEV_1 did not differ between the atropine pretreatment group and the nonpretreatment group. Thus atropine inhalation before ethanol challenge did not suppress the ethanol-induced reduction in FEV_1 . Two patients had marked dyspnea after ethanol challenge. Both received inhaled salbutamol sulfate during the study period.

DISCUSSION

The mechanism by which alcohol consumption exacerbates symptoms of bronchial asthma seems to involve IgE-mediated or other allergic responses

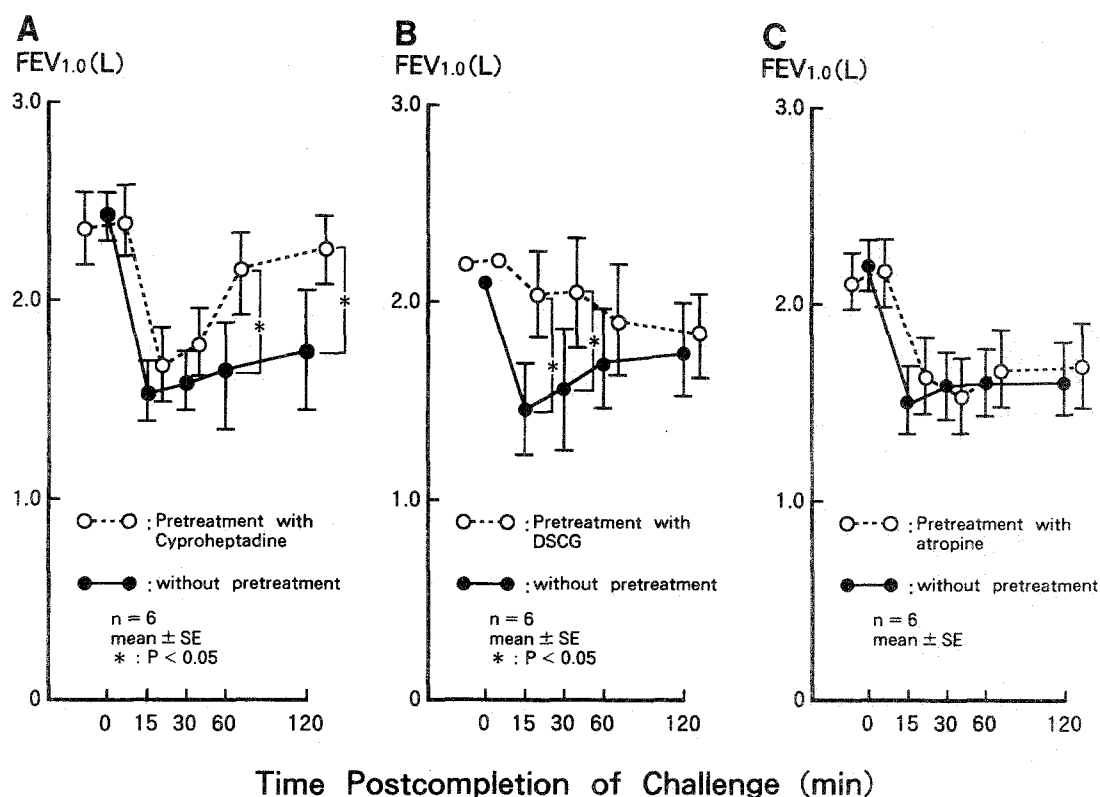


FIG. 9. Mean changes in FEV₁ after ethanol challenge after pretreatment with or without cyproheptadine (A), DSCG (B), and atropine (C).

to fungi, yeasts, hops, or other components of alcoholic beverages.^{16,17} It is also known that the preservatives and dyes contained in alcoholic beverages have induced asthma attacks through a mechanism resembling that of aspirin-induced asthma.^{16,18} If high concentrations of an alcoholic beverage are ingested or inhaled rapidly, they can induce bronchial attacks with a short latency period through their stimulation of the airway.^{1,2} In some cases, sulfur dioxide, contained in red wine, induces asthma attacks.¹⁹ Thus a variety of mechanisms may be involved in alcohol-induced exacerbations of asthma. However, few direct studies of the effects of alcohol itself on the exacerbation of asthma have been performed. The mechanism of alcohol-induced asthma, which is characteristic of Asians, and for which incidence varies markedly, also remains unknown. In this study, which was undertaken to clarify the mechanism of this phenomenon, we first carried out an oral ethanol challenge test. Of all patients, 54.8% responded positively to this test. This positive rate was lower than the percentage of the same patients who had responded to our survey that they had experienced asthma attacks after alcohol consumption. This

discrepancy is probably a result of the ethanol challenge test being carried out when the subjects were in a relatively stable condition, free of asthma attacks, whereas the positive rate in the survey also includes those cases in which alcohol consumption during a slight worsening of their disease resulted in the onset of asthma attacks.

In terms of blood ethanol level after ethanol challenge, there was no significant difference between responders and nonresponders. On the other hand, blood acetaldehyde level in responders was significantly higher than that in nonresponders for a period between 15 and 60 minutes after ethanol challenge. Blood histamine level was also significantly higher in responders than in nonresponders. The time course of blood acetaldehyde level (Fig. 4) and blood histamine level (Fig. 5) was identical to the course of FEV₁, which decreased after ethanol challenge in the responders. These results suggest that alcohol-induced bronchial asthma is more closely related to acetaldehyde (a metabolite of ethanol) than to ethanol itself.

The leukocyte histamine release test revealed no histamine release induced by physiologic concentrations of ethanol. On the other hand, acetalde-

hyde was found to promote histamine release in a concentration-dependent manner. In this test, no significant difference was observed in histamine release after stimulation with a low concentration of acetaldehyde between the control subjects and patients with asthma. After stimulation with a high concentration of acetaldehyde, a significant difference was observed in the histamine release rate. These findings suggest that the leukocyte reactivity to acetaldehyde was increased with an increase in the acetaldehyde concentration in the asthmatic patients, regardless of whether they were responders or nonresponders, compared with the control subjects. Further studies on the time course of histamine release after acetaldehyde stimulation may provide more interesting data. If this finding is combined with the results of the oral ethanol challenge test, it appears that ethanol challenge elevated blood acetaldehyde levels more intensely in responders than the same challenge in nonresponders and that this change induced massive histamine release in responders, resulting in asthma attacks.

The ELISA, in which acetaldehyde-HSA conjugate was used as an antigen, did not detect IgE specific to this conjugate in patients with asthma. This result suggests that IgE antibodies are not involved in acetaldehyde-induced histamine release.

These results allow us to estimate the following mechanism of alcohol-induced bronchial asthma; that is, the abnormal elevation in acetaldehyde level after alcohol consumption and the elevated leukocyte responses to acetaldehyde in patients with asthma induced massive histamine release, which contracts the airway smooth muscles (an asthma attack). The hypersensitivity of the airway to histamine and other nonspecific stimuli, which is usually observed in patients with asthma, is also involved in the onset of asthma attacks after alcohol consumption.

The results also suggest that basophils or mast cells and the histamine released from these cells are involved in the airway constriction after alcohol consumption. We speculated that antihistamines and agents that inhibit the release of chemical mediators might suppress this response to alcohol. On the basis of this assumption, we then assessed the effects of several drugs of these classes on alcohol-induced asthma.

Cyproheptadine, which is known to possess an antihistamine action, suppressed the responses of patients with asthma to ethanol between 60 and 120 minutes after ethanol challenge. DSCG, which

inhibits the release of chemical mediators from mast cells, significantly suppressed the responses in early stages (between 15 and 30 minutes) after ethanol challenge. These results suggest that histamine (a chemical mediator) is involved in alcohol-induced asthma and that the mast cells of the airway, which is exposed to inhaled DSCG, are also involved in alcohol-induced asthma. Cyproheptadine did not suppress early responses (between 15 and 30 minutes), and DSCG did not suppress the late responses (between 60 and 120 minutes). Thus neither of these two agents completely suppressed ethanol-induced airway constriction. This result suggests that the actions of these drugs were not strong enough to inhibit the histamine release or the pharmacologic actions of histamine completely.

Cyproheptadine, an H_1 -receptor antagonist, also has calcium channel antagonistic action, antiserotonin action, and anticholinergic action. Therefore the use of cyproheptadine as an H_1 -receptor antagonist in this study may have been somewhat problematic. However, histamine was definitely released by acetaldehyde stimulation. The partial suppression of histamine release by cyproheptadine suggests that the main action of cyproheptadine is antihistamine action. Regarding cyproheptadine, which was orally administered to subjects 40 minutes before ethanol challenge, it is possible that the intestinal absorption of this drug varies among individuals and that the blood cyproheptadine level had not reached its effective level 15 to 30 minutes after ethanol challenge when the patients showed maximal airway constriction. Factors such as the time of oral cyproheptadine administration, digestion, or respiration may have affected results. Although histamine was the only chemical mediator examined in this study, it is possible that some other chemical mediators are released in response to ethanol challenge. This may be another reason for the incomplete suppression of ethanol-induced asthma by the antihistamine alone. In this regard, it seems necessary to study additional cases and to modify the method of antihistamine administration by using other effective antihistamine drugs so that accurate blood levels can be obtained 15 to 30 minutes after ethanol challenge.

Acetaldehyde, yielded from absorbed ethanol, is thought to be primarily present in blood and to induce the release of histamine from basophils in circulating blood. Some acetaldehyde is also present in pulmonary circulation and spreads through the airway.²⁰ Acetaldehyde in the pulmonary circulation is thought to induce the release of histamine from the mast cells of the airway mucosa, resulting

in constriction of the airway. Inhalation of DSCG inhibits the effects of acetaldehyde on airway mast cells, but it does not affect basophils in circulating blood. The action of histamine released from basophils is not inhibited by DSCG. This is probably the reason that the inhibitory effect of DSCG was incomplete in this study.

Airway constriction, which is observed after alcohol consumption, may be attributable to a direct action of inhaled alcohol (ethanol) vapors or aroma on the airway irritant receptors. This route of airway stimulation, however, did not seem to be closely involved in alcohol-induced bronchial asthma in this study because atropine inhalation did not inhibit asthma attacks and because this mechanism cannot explain the racial specificity of alcohol-induced asthma. Some patients with alcohol-induced bronchial asthma receive prophylactic β -stimulant inhalation therapy before they consume alcohol, primarily for its effects in inducing nonspecific dilation of smooth muscles.

Aldehyde dehydrogenase (ALDH) is an enzyme that catalyzes the decomposition of acetaldehyde. ALDH2, found in the mitochondrial fraction, is a major ALDH isozyme involved in acetaldehyde metabolism. It has been reported that the blood acetaldehyde level after consumption of whiskey (1 ml/kg body weight) was much higher in individuals with a reduced ALDH2 activity (35.4 $\mu\text{mol/L}$) than in individuals with a normal ALDH2 activity (2.1 $\mu\text{mol/L}$), and that it was about 20 times the normal level in patients with homozygous ALDH2 deficiency (95.0 $\mu\text{mol/L}$).^{21, 22} Harada et al.²¹ investigated the polymorphism of ALDH2 among different races and nations and reported that the incidence of ALDH2 anomaly was much higher for Japanese (42.6%) than for Caucasians (0%). The racial specificity of alcohol-induced bronchial asthma seems to be closely related to ALDH2 anomaly for the following reasons: (1) the incidence of ALDH2 anomaly in Japanese patients is close to the percentage of patients with asthma who responded positively to the ethanol challenge test in this study; and (2) the peak blood acetaldehyde level in patients with ALDH2 anomaly, reported by Harada et al.,²¹ is close to the peak blood acetaldehyde level of patients with alcohol-induced asthma in this study. In the future, a genetic study of this relationship is needed.

On the basis of findings from this and previous studies, we propose the following mechanism of alcohol-induced bronchial asthma. Ethanol, ingested orally, is decomposed by alcohol dehydrogenase to yield acetaldehyde, which is then de-

graded by acetaldehyde dehydrogenase (ALDH) to yield acetic acid. In cases in which an inactive type of ALDH2 prevails (as is often the case in Japanese patients), blood acetaldehyde levels are elevated after alcohol consumption, which induces degranulation of basophils or mast cells and the release of chemical mediators (primarily histamine) from these cells, resulting in asthma attacks or facial hot flushes.

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