

Aerosolized acetaldehyde, but not ethanol, induces histamine-mediated bronchoconstriction in guinea-pigs

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Summary

It was reported that ethanol-induced bronchoconstriction was associated with elevated serum levels of acetaldehyde and histamine in Japanese asthmatic patients, but there is no study to investigate the airway response to acetaldehyde. We performed this animal study to test the hypothesis that acetaldehyde has the bronchospastic action via histamine release. First, we investigated the airway response to ascending doses (31.3, 62.5, 125, and 250 mM) of inhaled ethanol or acetaldehyde in guinea-pigs. Secondly, guinea-pigs pretreated with intraperitoneal injection of saline or 20 mg/kg diphenhydramine inhaled acetaldehyde. Finally, guinea-pigs pretreated with intraperitoneal injection of saline or 0.5 mg/kg atropine sulfate inhaled acetaldehyde. Inhalation of acetaldehyde, but not ethanol, caused bronchoconstriction in a dose-dependent manner. The bronchoconstriction induced by inhaled acetaldehyde was completely prevented by pretreatment with diphenhydramine. Atropine had no preventing effect against the acetaldehyde-induced bronchoconstriction. In conclusion, acetaldehyde has the bronchospastic action via histamine release in guinea-pigs. It is suggested that histamine H₁-antagonists may be available for preventing alcohol-induced asthma.

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Introduction

Exacerbation of asthmatic symptoms has been observed among 55% of Japanese asthmatic patients [1] and other Mongoloids after drinking ethanol [2,3]. On the other hand, a number of authors have reported that Japanese and other Mongoloids show a marked flush and other vasomotor symptoms after alcohol intake [4–7], which is associated with lack of aldehyde dehydrogenase (ALDH) [8]. ALDH consists of two main isozymes with low and high *K_m* for aldehyde [9–11]. About 50% of Japanese, who lack the low *K_m* enzyme (ALDH 2), show an elevation of serum acetaldehyde concentration due to their inability to metabolize acetaldehyde quickly and effectively [12–14]. Both exacerbation of asthmatic symptoms and vasomotor symptoms after drinking alcoholic beverages have not been shown in Caucasoids. It suggests that ethanol-induced bronchoconstriction associates with acetaldehyde. Recently, Watanabe [1] demonstrated that blood acetaldehyde and histamine concentrations in

asthmatics with alcohol-induced bronchoconstriction increased after ingestion of ethanol, and that acetaldehyde caused histamine release from leukocytes in asthmatics *in vitro*.

However, the effect of ethanol and acetaldehyde on the airways is unknown. Therefore we performed this animal study to test the hypothesis that acetaldehyde has the bronchospastic action via histamine release.

Materials and methods

Preparation of animals

Male albino Hartley strain guinea-pigs (350–400 g) were anaesthetized intraperitoneally by an injection of 75 mg/kg of sodium pentobarbital. They were placed in the supine position and the trachea was cannulated with polyethylene tube (outside diameter, 2.5 mm; inside diameter, 2.1 mm).

After surgery, the guinea-pig was artificially ventilated by a small animal respirator (Model 1680, Harvard Apparatus Co., Inc., South Natick, Ma, U.S.A.) adjusted to a tidal volume of 10 ml/kg at a rate of 60 strokes/min. The changes in lung resistance to inflation, the lateral

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pressure of tracheal tube (pressure at the airway opening; Pao) (cmH₂O), were measured by the modified method of Konzett and Roessler [15] described by Jones *et al.* [16] (Model TP-603T, Nihon Koden Kogyo Co, Ltd, Tokyo, Japan). Since the change in Pao following inhalation of leukotriene C₄ represented the average of the changes in pulmonary resistance (RL) and reciprocal dynamic lung compliance (1/C_{dyn}) [17], we have used Pao as an overall index of bronchial response to bronchoactive agents. The animals were overinflated by two times of tidal volume for two breaths by cramping the outlet port of the respirator to unify the volume history of the lung.

Airway response to inhaled ethanol and acetaldehyde

The aerosol was generated during a 15 sec period by an ultrasonic nebulizer developed for small animals at our institution [18]. The amount of aerosol was 15.2 µl/min and 46.4% of the aerosol was deposited in the lung as measured by the radioaerosol technique [18]. It was therefore calculated that about 1.76 µl of either ethanol or acetaldehyde solution was deposited in the lung during the 15 sec period. Saline 0.9% w/v was inhaled 15 min after the completion of animal preparation, when Pao had been stabilized. Five minutes later, 31.3 mM of either ethanol or acetaldehyde dissolved in 0.9% w/v saline was inhaled for 15 sec and Pao was continuously recorded. Every 5 min the same procedure was repeated except that either ethanol or acetaldehyde was administered in ascending dose (31.3, 62.5, 125, and 250 mM). Airway response to each concentration of either ethanol or acetaldehyde was determined as % increase in Pao compared with the value of Pao before first inhalation of 0.9% w/v saline.

Effect of diphenhydramine on airway response to inhaled acetaldehyde

Guinea-pigs were assigned into two groups depending on following treatments. Group 1 (control group) and Group 2 received intraperitoneal injection of 1.0 ml/kg of 0.9% w/v saline and 20 mg/ml/kg diphenhydramine dissolved in saline, respectively, 30 min before the anaesthesia. Inhalation of acetaldehyde was performed by the same procedure as mentioned above.

Effect of atropine sulfate on airway response to inhaled acetaldehyde

Guinea-pigs were assigned into two groups depending on following treatments. Group 1 (control group) and Group 2 received intraperitoneal injection of 1.0 ml/kg of 0.9% w/v saline and 0.5 mg/ml/kg atropine sulfate

dissolved in saline, respectively, 30 min before the anaesthesia. Inhalation of acetaldehyde was performed by the same procedure as mentioned above.

Statistical analysis

Statistical differences were determined by Mann-Whitney's *U*-test. Significance was based on a 95% confidence level ($P < 0.05$) and all measurements were expressed as mean $\pm$ s.e.m.

Chemicals

The following chemicals were used: sodium pentobarbital (Abbott Laboratories, North Chicago, IL, U.S.A.); ethanol (Wako Pure Chemical Ind., Osaka, Japan); acetaldehyde (Wako Pure Chemical Ind., Osaka, Japan); diphenhydramine (Wako Pure Chemical Ind., Osaka, Japan); atropine sulfate (Wako Pure Chemical Ind., Osaka, Japan).

Results

Airway response to inhaled ethanol and acetaldehyde (Fig. 1)

The mean Pao value before the first challenge of saline was 9.1 ± 0.1 and 9.3 ± 0.3 cmH₂O in ethanol group and acetaldehyde group, respectively, and there was no significant difference between these. Acetaldehyde inhalation provoked bronchoconstriction in a dose dependent manner, but there was no airway response to aerosol administration of each concentration of ethanol.

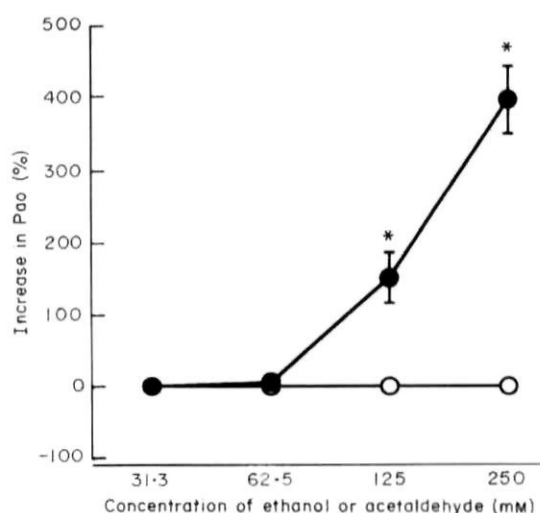


Fig. 1. Dose response curve of % increase in pressure at the airway opening (Pao) induced by aerosolized ethanol (○) ($n = 6$) and acetaldehyde (●) ($n = 6$) in artificially ventilated and anaesthetized guinea-pigs. Each point represents the mean value ($\pm$ SEM). *: $P < 0.005$ compared with ethanol.

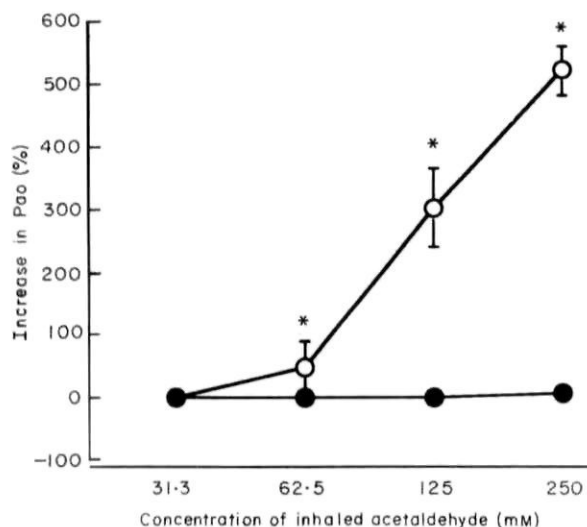


Fig. 2. Dose response curve of % increase in pressure at the airway opening (Pao) induced by aerosolized acetaldehyde in artificially ventilated and anaesthetized guinea-pigs pretreated with intraperitoneal saline (○) ($n=6$) or diphenhydramine injection (●) ($n=7$) 30 min before anaesthesia. Each point represents the mean value ($\pm$ s.e.m.). *: $P < 0.002$ compared with the diphenhydramine-treated group.

Inhibitory effect of diphenhydramine on airway response to inhaled acetaldehyde (Fig. 2)

The mean Pao value before the first challenge of saline was 9.0 ± 0.2 and 9.0 ± 0.2 cmH₂O in Group 1 (control group) and Group 2 (pretreated with diphenhydramine),

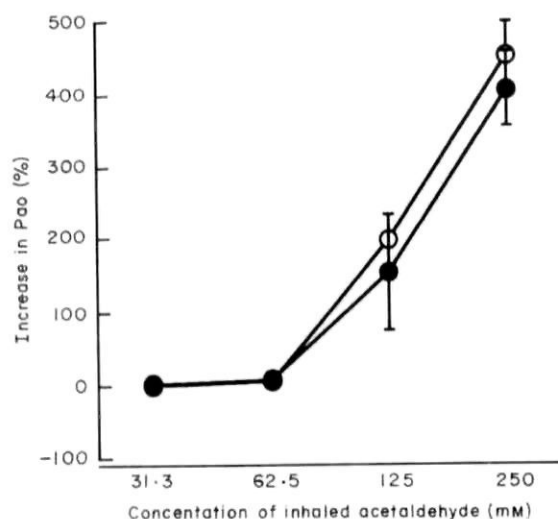


Fig. 3. Dose response curve of % increase in pressure at the airway opening (Pao) induced by aerosolized acetaldehyde in artificially ventilated and anaesthetized guinea-pigs pretreated with intraperitoneal saline (○) ($n=6$) or atropine sulfate injection (●) ($n=6$) 30 min before anaesthesia. Each point represents the mean value ($\pm$ s.e.m.).

respectively, and there was no difference between these. Increase in Pao induced by aerosol administration of acetaldehyde was completely prevented by pretreatment with diphenhydramine.

Inhibitory effect of atropine sulfate on airway response to inhaled acetaldehyde (Fig. 3)

The mean Pao value before the first challenge of saline was 9.1 ± 0.3 and 9.1 ± 0.2 cmH₂O in Group 1 (control group) and Group 2 (pretreated with atropine sulfate), respectively, and there was no significant difference between these. Pretreatment with atropine sulfate did not affect the increase in Pao induced by aerosol administration of acetaldehyde.

Discussion

In this study, we investigated the airway response to aerosol administration of acetaldehyde in guinea-pigs. It has been reported that acetaldehyde increases the blood and urine levels of catecholamines in animals [19–21]. In this study, we chose aerosol administration of acetaldehyde in order to examine the direct effect of acetaldehyde on airways, excluding the sympathomimetic action and effect of ALDH.

Alcohol is oxidized to acetaldehyde. Blood acetaldehyde level in some asthmatics whose FEV₁ fell more than 20% after ingestion of ethanol were significantly higher than those in other asthmatics whose FEV₁ fell less than 20% after ingestion of ethanol, while there was no significant difference in blood ethanol level between them [1]. At the first, therefore, we examined whether inhalation of either ethanol or acetaldehyde induces bronchoconstriction in guinea-pigs. Our data (Fig. 1) showed that inhalation of acetaldehyde causes dose-dependent increase in Pao, but there was no airway response to inhalation of ethanol. It is possible that acetaldehyde has a important role in ethanol-induced bronchoconstriction.

It has been reported that pretreatment with cromolyn sodium has no inhibitory effect on the alcohol-induced bronchoconstriction [2,3], whereas Gong *et al.* [3] reported a case of an asthmatic Asian showing alcohol-induced bronchoconstriction, in whom a cyproheptadine had a partial inhibitory effect on the alcohol-induced bronchoconstriction. In addition, Watanabe [1] reported that acetaldehyde caused concentration-dependent histamine release from leucocytes in asthmatics *in vitro*. Secondly, therefore, we investigated whether acetaldehyde-induced bronchoconstriction is caused by releasing histamine or not. As a result (Fig. 2), increase in Pao was completely prevented by pretreatment with diphenhydramine.

Diphenhydramine has some anti-muscarinic action, and it was reported that atropine had a partial inhibitory effect on the alcohol-induced bronchoconstriction [3]. Consequently, we examined whether the inhibitory effect of diphenhydramine results from the anti-muscarinic effect or not. Finally, as shown in the results section (Fig. 3), as atropine had no preventing effect on the acetaldehyde-induced bronchoconstriction, we conclude that acetaldehyde causes bronchoconstriction indirectly via histamine release in guinea-pigs.

Korsten *et al.* [22] reported that mean acetaldehyde plateau levels of blood of alcoholics was at 42 μM . Because the concentrations of inhaled acetaldehyde in our study were 31.3–250 mm , we cannot define the mechanisms of alcohol-induced bronchoconstriction. However, our results that inhaled acetaldehyde caused histamine-mediated bronchoconstriction in guinea-pigs might in the future help to guide human studies that could define the mechanism of alcohol-induced bronchoconstriction.

In conclusion, acetaldehyde has bronchospastic action via histamine release in guinea-pigs, and we believe that this animal study may lead to better design in future work on humans that will clarify the mechanism of ethanol-induced bronchoconstriction.

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