Contribution of Gastric Emptying to the Blood Ethanol-Lowering Effect of Acetic Acid

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Blood ethanol concentrations are decreased by the oral administration of ethanol with acetic acid. The slowing of gastric emptying is supposed to be one of the mechanisms for the blood ethanol-lowering effect. In the present study, to further clarify the contribution of gastric emptying to this effect, we investigated the blood ethanol concentration, and the amounts of ethanol remaining in the stomach and in the small intestine, after orally administering ethanol with acetic acid or various salts of acetic acid. This was done under two conditions in which the osmolarity or concentration of the acetate ion in each administered solution was equalized.

The blood ethanol-lowering effect of acetic acid was weakened by replacing acetic acid with sodium, potassium, or calcium acetate. There was a good negative correlation between the blood ethanol concentration and the amount of ethanol remaining in the stomach one hour after administering the sample solutions. The amount of ethanol remaining in the small intestine was not increased in the acetic acid group. From these results, the slowing of gastric emptying is considered to be the major mechanism for the blood ethanol-lowering effect of acetic acid, and is presumed to be controlled by cations of the solution, and not by the acetate ion.

It has been reported that blood ethanol concentrations were decreased when ethanol was orally administered with such organic acids as acetic acid, lactic acid or citric acid. Acetic acid had the strongest blood ethanol-lowering effect of the previously investigated organic acids. Vinegar, in which the major components are organic acids, also showed a strong lowering effect.1)

Orally administered ethanol is absorbed through the digestive tract,2) enters the systemic circulation, and most of the absorbed ethanol is metabolized in the liver.3,4) The absorption and metabolism of ethanol must be considered as the factors which control the blood ethanol concentration. It was clarified that the gastric emptying of ethanol was delayed by the administration of acetic acid, and this was suggested to be one of the mechanisms for the blood ethanol-lowering effect.5) In the previous study,5) because acetic acid was administered as free acid, it was not clear whether the acetate ion or cation was important for slowing the gastric emptying. Also, the concentration of each administered solution was not examined sufficiently well.

In the present study, we attempt to elucidate the role of gastric emptying on the blood ethanol-lowering effect of acetic acid by using various salts of acetic acid under condition in which the osmolarity or the concentration of the acetate ion in the administered solution was equalized.

Materials and Methods

Male Sprague-Dawley rats (Seiwa Laboratory Animal Center, Fukuoka, Japan) were used. The animals were fed on a stock diet (MF, Oriental Yeast Industry Co., Ltd., Tokyo, Japan), food and water being withdrawn overnight before the experiments. In Experiments 1 and 2, rats weighing about 200 g were used, and in Experiments 3 and 4, rats weighing about 350 g were used. The rats were administered via a stomach tube with 10 ml/kg of 20 w/v % ethanol solutions containing various concentrations of
acetic acid or salts of acetic acid. Sodium chloride was added to the control solution, and acetic acid, sodium acetate, potassium acetate, or calcium acetate (Wako Pure Chemical Co., Ltd., Osaka, Japan) was added to the test solution. The blood ethanol concentrations were determined by a commercial kit using the enzymatic method (F-kit Ethanol, Boehringer–Mannheim–Yamanouchi Co., Ltd., Tokyo, Japan) after deproteinizing by 0.33 N perchloric acid. The remaining ethanol in the stomach and small intestine was also determined by the enzymatic method.

**Experiment 1.** Test solutions were prepared as equiosmolar concentrations of the contained acid of salts. Namely, the concentrations of acetic acid and the salts of acetic acid were 290 mOsmol/l. After administering, blood was collected via the tail vein, and the blood ethanol concentration was determined.

**Experiment 2.** Test solutions were prepared as equimolar concentrations of the acetate ion (290 mmol/l). Blood was collected, and the blood ethanol concentration was determined.

**Experiment 3.** This was done to clarify the relationship between blood ethanol concentration and the remaining ethanol in the stomach or in the small intestine after administering an ethanol solution containing various salts of acetic acid which had equal osmolarities. The administered solutions were the same as those in Experiment 1. One hour after intubation, the rats were decapitated, and the stomach and small intestine removed. The remaining ethanol in the stomach and in the small intestine was determined.

**Experiment 4.** This was done to clarify the relationship between blood ethanol concentration and the remaining ethanol in the stomach and small intestine after administering an ethanol solution containing various salts of acetic acid which had equal concentrations of the acetate ion. The administered solutions were the same as those in Experiment 2, and the other conditions were the same as those in Experiment 3.

The statistical significance of difference was assessed by ANOVA and then by Tukey's multiple range test.6)

**Results**

The time courses of blood ethanol concentration after an oral administration to the rats of ethanol with various salts of acetic acid are shown in Fig. 1A (Exp. 1) and Fig. 1B (Exp. 2). In Experiment 1, the blood ethanol concentration in the acetic acid group was lower than that of the control each time. The blood ethanol concentrations in the sodium, potassium and calcium acetate groups were lower than that of the control immediately after administering the solutions, but subsequent levels of blood ethanol were identical to those of the control. In Experiment 2, the blood ethanol concentration in the acetic acid group

| Table I. Blood Ethanol Concentration and the Ratio of Ethanol Remaining in the Stomach and in the Small Intestine per Administered Ethanol Quantity 1 hr after Orally Administering 10 ml/kg of a 20 w/v% Ethanol Solution in Saline (Control) and 290 mOsmol/l of Various Salts of Acetic Acid in Experiment 3 |
|-----------------|-----------------|-------------------|
| Group           | Blood ethanol (mg/100 ml) | Remaining ethanol ( % of doses) |
| Control         | 89±25**         | 34.7±7.8a         | 0.78±0.14ab |
| Acetic acid     | 54±23ab         | 68.0±4.4b         | 0.26±0.06a  |
| Na acetate      | 70±23b          | 40.1±8.2a         | 1.00±0.33ab |
| K acetate       | 43±11b          | 50.8±5.9ab        | 0.26±0.08a  |

* Mean±SEM (n=5). Means within a column not followed by the same letter are significantly different (p<0.05).

| Table II. Blood Ethanol Concentration and the Ratio of Ethanol Remaining in the Stomach and in the Small Intestine per Administered Ethanol Quantity 1 hr after Orally Administering 10 ml/kg of a 20 w/v% Ethanol Solution in Saline (Control) and 290 mOsmol/l of Acetate Ion Supplied by Various Salts of Acetic Acid in Experiment 4 |
|-----------------|-----------------|-------------------|
| Group           | Blood ethanol (mg/100 ml) | Remaining ethanol ( % of doses) |
| Control         | 117±19**        | 37.5±8.8a         | 1.51±0.31ab |
| Acetic acid     | 23±4c           | 68.9±2.6b         | 1.43±0.34ab |
| Na acetate      | 100±12a        | 40.9±2.7a         | 0.87±0.23b  |
| K acetate       | 73±10c          | 56.0±2.2b         | 0.96±0.32ab |
| Ca acetate      | 23±14b          | 63.7±3.0b         | 2.10±0.51a  |

* Mean±SEM (n=4–5). Means within a column not followed by the same letter are significantly different (p<0.05).
was also lowered. The blood ethanol concentrations in the sodium and potassium acetate groups were lower than those of the control one and two hours after intubation, but the subsequent levels were identical with those of the control. Calcium acetate had a stronger effect on blood ethanol-lowering than sodium or potassium acetate, but the effect of calcium acetate was not equal to that of acetic acid. The results of blood ethanol concentration and the remaining ethanol in the stomach and small intestine, which are expressed as the % of doses, one hour after intubation in Experiments 3 and 4 are presented in Tables I and II. In both experiments, the amount of ethanol remaining in the stomach was much greater in the acetic acid group, which had a remarkable blood ethanol-lowering effect. The amount of ethanol remaining in the stomach varied with the various salts of the acetic acid groups. The amount of ethanol remaining in the small intestine was not significantly increased in the acetic acid group, and there was no characteristic trend for this in any group.

The relationship between the blood ethanol concentration and the amount of ethanol remaining in the stomach one hour after intubation of a sample solution is shown in Fig. 2A (Exp. 3) and Fig. 2B (Exp. 4). Under both conditions, in which the osmolarity (Exp. 3) or the concentration of the acetate ion (Exp. 4) in the administered solutions was equalized,
there was a good negative correlation between the blood ethanol concentration and the amount of ethanol remaining in the stomach.

**Discussion**

It is known that the blood ethanol concentration declined when rats were orally administered with ethanol and acetic acid. Such a lowering effect is common to some organic acids, acetic acid having had the strongest effect in previously investigated organic acids.\(^1\) The slowing of gastric emptying of ethanol was suggested to be one of the mechanisms for the blood ethanol-lowering effect of acetic acid in a previous study,\(^5\) in which ethanol was orally administered with vinegar.

The plasma glucose-flattening activity of such dietary fiber as pectin or guar gum was thought to be due to the slowing of gastric emptying of glucose.\(^7,8\) The blood glucose-lowering effect of organic acids was also presumed to involve the slowing of gastric emptying as one of the mechanisms.\(^9,10\)

The osmolarity\(^11\) and the energy content\(^12,13\) of an administered solution influence gastric emptying, so we examined the effect under two conditions in which the osmolarity and the concentration of the acetate ion in the administered solutions were equalized. In the present study, the lowering effect of acetic acid was weakened by replacing acetic acid with a salt of acetic acid such as sodium, potassium, or calcium acetate (Figs. 1A and 1B). There was a good negative correlation between the blood ethanol concentration and the amount of ethanol remaining in the stomach (Figs. 2A and 2B). The differences in the degree of the blood ethanol-lowering effect by the administration of acetic acid and various salts of acetic acid is presumed to have been caused by the different rates of gastric emptying. Because a change in the rate of gastric emptying was observed when the concentration of the acetate ion in the administered solution was equalized in Experiment 4, we supposed that cations of the solution, and not the acetate ion, might control the rates of gastric emptying. Hunt and Knox\(^14\) have reported that the rate of gastric emptying was changed by administering
various salts of citric acid. The slowing of gastric emptying influences the rate of the absorption of ethanol.\textsuperscript{15}) Blood ethanol concentration is fixed by the balance between the amount of absorbed ethanol and that metabolized. Consequently, the slowing of the rate of ethanol absorption due to slowing of gastric emptying might bring about a blood ethanol-lowering effect.

Administered ethanol is absorbed from the digestive tract\textsuperscript{2}) and mainly metabolized in the liver.\textsuperscript{3,4)} The factors which control the blood ethanol level are thought to be a change in the velocity of ethanol absorption from the small intestine and/or the ethanol metabolism in the liver, apart from the gastric emptying of ethanol. In the present study, the amount of ethanol remaining in the small intestine was not increased in the acetic acid group (Tables and I and II). No correlation between the blood ethanol concentration and the amount of ethanol remaining in the small intestine in both experiments 3 and 4 was found. In respect of the metabolism of ethanol in the liver, Tachiyashiki \textit{et al.}\textsuperscript{16)} have reported that the activity of liver alcohol dehydrogenase (ADH) was not changed by the administration of ethanol with acetic acid under almost the same condition as ours. Therefore, inhibition of the absorption of ethanol from the small intestine and/or promotion of the metabolism of ethanol in the liver may not be the mechanisms for the blood ethanol-lowering effect of acetic acid. Instead, the slowing of gastric emptying may be the major mechanism for the effect. However, not only the rate of absorption of ethanol may be affected by the slowing of gastric emptying. Lieber \textit{et al.}\textsuperscript{17–19)} described that a part of orally administered ethanol was oxidized in the stomach before absorption. The longer ethanol remains in the stomach, the more the amount of oxidized ethanol may increase before entering the systemic circulation. From the results shown in Figs. 1A and 1B, it can be interpreted that the amount of ethanol entering the systemic circulation was decreased by the administration of acetic acid. There is a possibility that this may be one of the factors for the blood ethanol-lowering effect, and we intend to investigate this point further.

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\textbf{References}

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