

# Influence of Drinking Conditions on Alcohol Metabolism in Healthy Men with *ALDH2*\*1/\*1 Genotype: Comparison between Different Alcoholic Drinks with or without Meal

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## ABSTRACT

The influence of drinking conditions on alcohol metabolism and drunkenness was investigated in healthy men with *ALDH2*\*1/\*1 genotype aged from 40 to 60 who were occasional or habitual drinkers. The investigation was performed by open intersection competitive drinking tests at an ethanol dose of 0.32 g/kg under 4 different drinking conditions: beer without a meal [B(-)], shochu (a distilled spirit) without a meal [S(-)], beer with a meal [B(+)] and shochu with a meal [S(+)]. The blood alcohol concentration (BAC) and BAC-AUC (area under the curve) were lower in the B(-) than in the S(-). The blood acetaldehyde concentration (BAcH) and the serum acetate concentration (SAce) were also lower in the B(-) than in the S(-). The meal markedly decreased BAC, BAC-AUC and BAcH-AUC for both alcoholic beverages. Subjective drunkenness was stronger in order of B(+) < S(+) < B(-) < S(-), depending on BAC. Ethanol degradation rate (EDR: mg/kg/h) was higher in order of S(-) < B(-) < S(+) < B(+), which may be caused by differences in the numbers of glucide calories in the drinking conditions because some glucide is contained in beer (3.0 g/100ml) but not in the spirit shochu. The ratio of lactic acid to pyruvic acid in the blood, which reflects the ratio of NADH/NAD<sup>+</sup> in liver cells, was higher in the S(-) than in the B(-), and was decreased by the meal for both alcoholic beverages. These results suggested that glucide increase the rate of alcohol metabolism by supplying pyruvic acid to decrease the ratio of NADH/NAD<sup>+</sup>, which lowers BAC and relieves drunkenness. Thus, the intake of glucide calories while drinking is important to reduce the pharmacological and toxicological actions of alcohol.

**Keywords:** Drinking Condition; *ALDH2* Genotype; Meal; Ratio of NADH/NAD<sup>+</sup>; Alcohol Metabolism

## 1. Introduction

Individuals drink alcohol in daily life under various conditions, which differ in terms of the kinds of alcoholic beverage, amounts drunk, meal conditions, age, sex, inherited alcoholic sensitivities, drinking customs, and physical or mental conditions, among others. These various drinking conditions modulate the influence of alcohol on the body. In order to consider metabolic disorders that induce organ damage and behavioral disorders through drinking, it is important to determine how these various conditions of drinking modulate the effects of alcohol on pharmacokinetics of blood alcohol and drunkenness.

However, there are limited data available on the daily drinking conditions of individual, combined with various individual conditions, although there are several reports on the influence of a meal on ethanol metabolism [1-8]. Therefore, in this study, we investigated how the differ-

ences in daily drinking conditions of individuals affect the pharmacokinetics of blood alcohol and drunkenness. We selected healthy Japanese men with *ALDH2*\*1/\*1 genotype and gave them alcohol at a moderate dose as beer or distilled shochu with or without a meal. The ultimate purpose of this study is to build a database of physiological, pharmacological and pathological changes in Japanese under different drinking conditions.

## 2. Subjects and Method

### 2.1. Subjects and Drinking Conditions

Fifteen healthy men took part in these experiments as paid volunteers, who were aged  $45.5 \pm 4.3$  years (range: 41 - 54 years) and weighed  $69.7 \pm 6.8$  kg (range: 57.7 - 81.0 kg). All of them have the *ALDH2* genotype of *ALDH2*\*1/\*1, while the *ADH1B* genotypes were follows: *ADH1B*\*1/\*1 type, 1; *ADH1B*\*1/\*2 type, 2; *ADH1B*\*2/\*2 type, 12. The alcohol consumption of the 15 subjects was

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69.6 ± 46.7 g/day (14.0 - 165.1 g/day) or 487.5 ± 327.0 g/week (98.0 - 1155.8 g/week). Among the 15 subjects, four were daily drinkers, who drank 113.2 ± 48.7 g of alcohol/day (68.0 - 165.1) or 792.3 ± 340.6 g of alcohol/week (529.2 - 1155.8). Two of the four daily drinkers had drunk for 20 years at 71.8 ± 5.4 g of alcohol/day (68.0 - 75.6) or 502.6 ± 37.6 g of alcohol/week (529.2 - 1155.8). Three were habitual drinkers, who drank 5 or 6 days per week and their consumption of alcohol was 84.5 ± 31.9 g/day (49.6 - 112.0) or 591.7 ± 223.0 g/week (347.2 - 784.0). The remaining eight were occasional drinkers, who drank on 4 days or less per week; their consumption of alcohol was 42.3 ± 32.0 g/day (14.0 - 100.4) or 296.1 ± 224.3 g/week (98.0 - 702.8).

The subjects refrained from alcohol and drugs for two days, and from eating and drinking except water for at least 12 hours before the test. This examination was performed by opening intersection competitive examinations on 4 drinking conditions: 1) the intake of beer without a meal [B(-)]; 2) the intake of shochu without a meal [S(-)]; 3) the intake of beer with a meal [B(+)] and 4) the intake of shochu with a meal [S(+)].

The experiment was started at 9:00, and subjects were served lunch 5 hr after the start of drinking. Smoking was not allowed during the experiment. The cleaning period was one week between one drinking condition and another condition.

The Medical Corporation WHA Ishii Clinic Research Ethics Committee approved the proposed study, and informed consent was obtained from every participant.

## 2.2. Administration of Alcohol to Subjects

The subjects received beer (5% v/v ethanol, 42 kcal/100 ml) or shochu (diluted to 16% v/v ethanol) at an ethanol dose of 0.32 g/kg body weight within 15 min. The test diet of the Diabetes Society (Kewpie Corporation, Japan) was served to the subjects as a meal. The meal included cream chicken, cracker and soft pudding, whose energy was 460 kcal, and the composition was as follows: protein: 18.0 g, lipid: 18.0 g, carbohydrate: 56.5 g, salt: 1.6 g.

## 2.3. Determination of Ethanol, Acetaldehyde, Acetate, Lactic Acid and Pyruvic Acid of the Blood

Blood samples were taken from a vein in the lower part of the elbow with a custody needle at 0, 0.5, 1, 2, 3, 4 and 5 hr after drinking, and the concentrations of blood ethanol (BAC) and acetaldehyde (BACH) were measured with a head-space gas chromatograph by the PCA/thiourea method, as previously reported [9,10].

Acetate in serum (SAce) was measured with an amino

acid analytical system (Shimadzu Corporation, Japan) after centrifugation of the blood.

Concentrations of lactic acid and pyruvic acid of serum were measured by a clinical examination company, SRL, Inc. (Japan).

## 2.4. Evaluation of Results

Blood-ethanol profiles were plotted for each subject and a set of parameters was worked out as described by Widmark [11]. Ethanol degradation rate (EDR; mg/kg/h) was calculated by dividing the dose of ethanol (0.32 g/kg) by the duration of alcohol metabolism (h), which was obtained from the x-intercept of a regression line fitted by the linear least-squares method to the blood alcohol concentrations from 1 h to 3 h after ethanol administration. The maximum BAC (BAC<sub>max</sub>) and the time (T<sub>max</sub>) to reach the peak of BAC were read from the BAC curves.

## 2.5. Subjective Drunkenness

The subjects filled out an interview sheet about several feelings of drunkenness by themselves. The degree of each feeling of drunkenness was periodically scored on a four-point scale (-: 0, ±: 1, +: 2, ++: 3) as a subjective drunkenness score. The subjective drunkenness score-AUC was calculated from the curve of the degree of subjective drunkenness score-time.

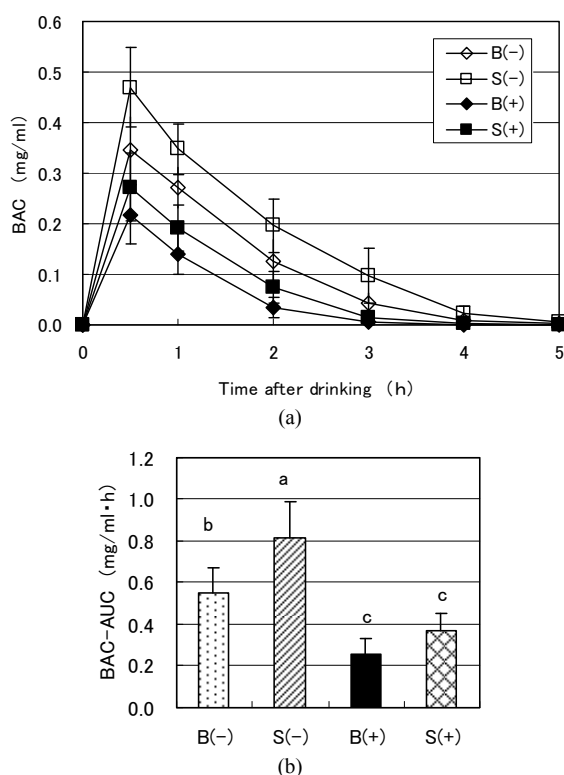
## 2.6. Statistics

Data are expressed as means ± SD and statistically analyzed by two-way analysis of variance (ANOVA) and Tukey's test using the standard statistical software SPSS, Version 12.0 (SPSS Japan Inc., Japan) or Steel-Dwass's test using Excel statistics (Microsoft Corporation). The difference was considered to be significant when *p* was <0.05.

## 3. Results

### 3.1. Blood Ethanol Profiles

As shown in **Figure 1(a)**, BAC was significantly higher in the S(-) than in the B(-). The meal significantly lowered BAC for both alcohol beverages (S(-) > B(-) > S(+) > B(+), *p* < 0.01 by ANOVA). BAC-area under the curve (BAC-AUC) also decreased in the same order of drinking conditions (**Figure 1(b)**, *p* < 0.01 by Tukey's test). Except for the B(+), the mean of BAC<sub>max</sub> in the three other drinking conditions exceeded 0.3 mg/ml with an ethanol dose of 0.32 g/kg, which is the lowest limit of BAC for legal driving in Japan. Among the 15 subjects, all subjects exceeded the legal BAC in the S(-), 11 in the B(-), 4 in the S(+) and 1 in the B(+) (**Figure 1(a)**).



Subjects ( $n = 15$ ) took beer (5% v/v ethanol) or shochu (16% v/v ethanol) at an ethanol dose of 0.32 g/kg of body weight within 15 min. In the meal intake condition, subjects took the test diet of the Diabetes Society (Kewpie Corporation, Japan) with alcoholic beverages. The data are expressed as mean  $\pm$  SD in each drinking condition.  $\diamond$ : beer intake [B(-)],  $\square$ : shochu intake [S(-)],  $\blacklozenge$ : beer + meal intake [B(+)],  $\blacksquare$ : shochu + meal intake [S(+)]. a, b and c: Means not sharing a common letter are significantly different among drinking conditions at  $p < 0.05$  by Tukey's test.

**Figure 1. Change of BAC (a) and BAC-AUC (b) in each drinking condition.**

EDR value was higher in the B(-) than in the S(-) and was increased by meal intake for both alcoholic beverages ( $p < 0.01$  by Tukey's test) ( $B(+) > S(+) > B(-) > S(-)$ ) and  $BAC_{max}$  was lower in the B(-) than in the S(-) and was decreased by meal intake for both alcoholic beverages ( $p < 0.01$  by Tukey's test) ( $S(-) > B(-) > S(+) > B(+)$ ) (Table 1). EDR showed a negative correlation with BAC-AUC (Figure 2;  $r = -0.9153$ ,  $p < 0.01$  by Pearson's test).

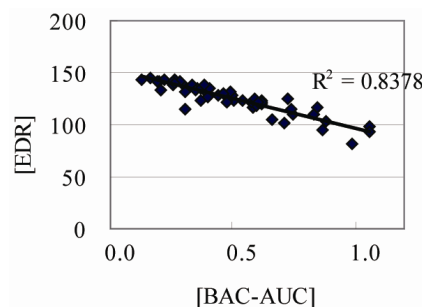
### 3.2. Blood Acetaldehyde Profiles

BAC<sub>H</sub> was higher in the S(-) than in the B(-) ( $p < 0.01$  by ANOVA) and was decreased significantly by meal intake for both beverages ( $p < 0.01$  by ANOVA). The order of BAC<sub>H</sub>-area under the curve (BAC<sub>H</sub>-AUC) was  $S(-) > S(+) > B(-) > B(+)$  (Figure 3(b)), differing from that of BAC-AUC (Figure 1(b);  $S(-) > B(-) > S(+) > B(+)$ ). The BAC<sub>H</sub>-AUC was the largest in the S(-) among

**Table 1. Comparison of parameters in ethanol metabolism among 4 drinking conditions.**

	BAC <sub>max</sub> (mg/ml)	EDR (mg/kg/h)
B(-)	0.35 $\pm$ 0.06	97.8 $\pm$ 6.8
S(-)	0.47 $\pm$ 0.08**	87.3 $\pm$ 11.1**
B(+)	0.22 $\pm$ 0.06**	111.7 $\pm$ 3.4**
S(+)	0.27 $\pm$ 0.07††	105.0 $\pm$ 6.3††#

Blood-ethanol profiles were plotted for each subject and a set of parameters was worked out as described in detail by Widmark. EDR (mg/kg/h) was calculated by dividing ethanol dose (0.32 g/kg) by the duration of alcohol metabolism, which was obtained from the x-intercept of a regression line fitted by the linear least-squares method to the blood alcohol concentrations from 1 hr to 3 hr after ethanol intake. The data are expressed as means  $\pm$  SD in each drinking condition. \*\*:  $p < 0.01$  vs B(-); ††:  $p < 0.01$  vs S(-); #:  $p < 0.05$  vs B(+)



**Figure 2. Correlation of BAC-AUC with EDR.**

the 4 drinking conditions (Figure 3(b); vs B(-) and B(+):  $p < 0.01$ , vs S(+):  $p < 0.05$ , by Tukey's test).

### 3.3. Serum Acetate Profiles

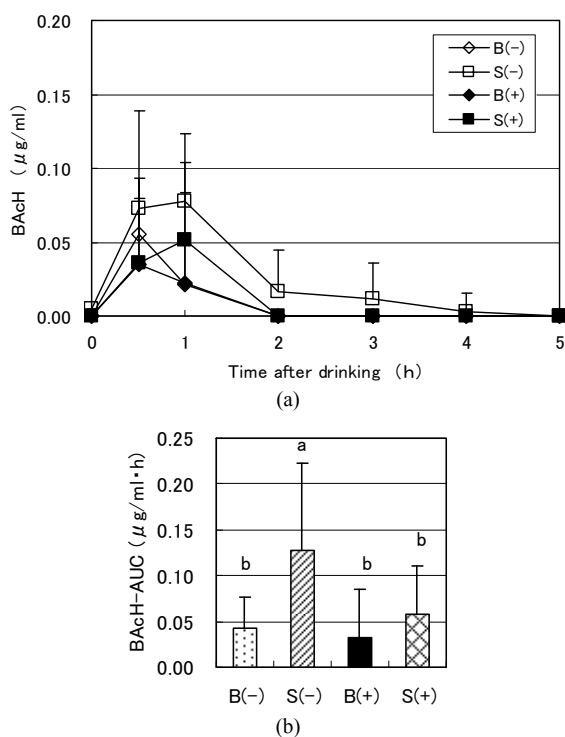
Although S<sub>ace</sub> was not significantly different among the 4 drinking conditions (Figure 4(a)), S<sub>ace</sub>-area under the curve (S<sub>ace</sub>-AUC) was smaller in the B(-) than in the S(-), B(+) and S(+)

### 3.4. Subjective Drunkenness Score

The subjective drunkenness score showed a time curve, reflecting that of BAC. The order of the subjective drunkenness score at  $T_{max}$  (30 min) was the same as that for BAC (Figures 1(a) and 5(a)). The subjective drunkenness score-AUC decreased in the order of  $S(-) > B(-) > S(+) > B(+)$  as well as that for BAC-AUC (Figures 5(a) and (b)).

### 3.5. Correlation among BAC, BAC<sub>H</sub>, S<sub>ace</sub> and Subjective Drunkenness Score

BAC, BAC<sub>H</sub> and S<sub>ace</sub> were significantly correlated with each other (BAC vs BAC<sub>H</sub>:  $r = 0.650$ , BAC vs S<sub>ace</sub>:  $r = 0.709$ , BAC<sub>H</sub> vs S<sub>ace</sub>:  $r = 0.399$ ,  $p < 0.01$ ). The concentrations of all these substances in the blood correlated



Subjects ( $n = 15$ ) took beer or shochu at an ethanol dose of 0.32 g/kg of body weight within 15 min. In the meal intake condition, subjects took the test diet of the Diabetes Society (Kewpie Corporation, Japan) with alcoholic beverages. The data are expressed as mean  $\pm$  SD in each drinking condition.  $\diamond$ : beer intake [B(-)],  $\square$ : shochu intake [S(-)],  $\blacklozenge$ : beer + meal intake [B(+)],  $\blacksquare$ : shochu + meal intake [S(+)]. a, b and c: Means not sharing a common letter are significantly different among drinking conditions at  $p < 0.05$  by Tukey's test.

**Figure 3. Changes of BACh (a) and BACh-AUC (b) in each drinking condition.**

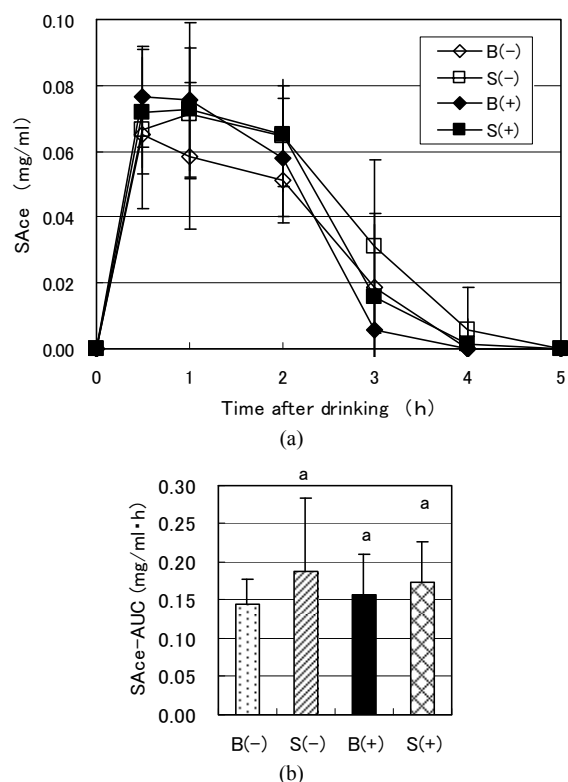
with the subjective drunkenness score (BAC:  $r = 0.507$ ,  $p < 0.01$ , SAce:  $r = 0.455$ ,  $p < 0.01$ , BACh:  $r = 0.255$ ,  $p < 0.01$  by Pearson's test).

### 3.6. Ratio of Lactic Acid to Pyruvic Acid Concentrations (L/P Ratio) in the Blood

The ratio of lactic acid to pyruvic acid concentrations in the serum (L/P ratio) showed a time change similar to that of BAC (Figure 6(a)). The ratio at 3 h after drinking decreased in the order of S(-) > B(-) > S(+) > B(+), and was strongly correlated with EDR value ( $r = -0.8785$ ,  $p < 0.01$  by Pearson's test) (Figure 6(b)).

## 4. Discussion

The aim of this study is to investigate the effects of different drinking conditions, in view of the fact that drinking is a daily practice for many Japanese, on the pharmacokinetics of blood alcohol, alcohol metabolism and drunkenness. At the first step of this study, we selected 15 healthy adult men who have *ALDH2*\*1/\*1 genotype



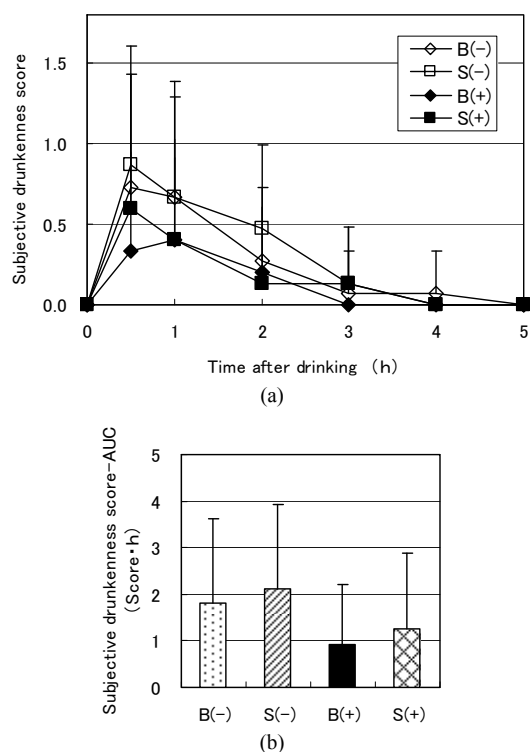
Subjects ( $n = 15$ ) took beer or shochu at an ethanol dose of 0.32 g/kg of body weight within 15 min. In the meal intake condition, subjects took the test diet of the Diabetes Society (Kewpie Corporation, Japan) with alcoholic beverages. The data are expressed as mean  $\pm$  SD in each drinking condition.  $\diamond$ : beer intake [B(-)],  $\square$ : shochu intake [S(-)],  $\blacklozenge$ : beer + meal intake [B(+)],  $\blacksquare$ : shochu + meal intake [S(+)]. a, b and c: Means not sharing a common letter are significantly different among drinking conditions at  $p < 0.05$  by Tukey's test.

**Figure 4. Changes of SAce (a) and SAce-AUC (b) in each drinking condition.**

and drink occasionally or habitually. They were given 0.32 g of ethanol/kg in 4 different drinking conditions: shochu (distilled spirit) without a meal [S(-)], beer (fermented beverage) without a meal [B(-)], shochu with a meal [S(+)] or beer with a meal [B(+)].

BAC in the S(-) with 16% ethanol was significantly higher than that in the B(-) with 5% ethanol, and the alcohol degradation rate in the body (EDR) was lower in the S(-) than that in the B(-). The difference of BAC between alcoholic beverages is generally considered to be due to the different rates of absorption of ethanol from digestive organs due to their different concentrations of ethanol [12].

Yokoyama *et al.* also reported that the ethanol concentrations in blood and saliva were significantly higher with wine (13% v/v ethanol) than with beer (5% v/v ethanol) at the same dose of ethanol (0.6 g/kg body weight) [13]. However, Risto could not demonstrate a difference in BAC when subjects were given 4% or 16%



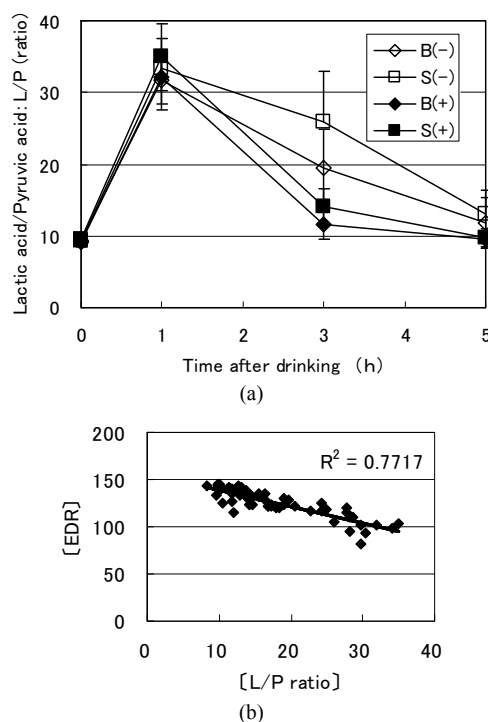
Subjective drunkenness score was obtained by asking questions. The data are expressed as means  $\pm$  SD in each drinking condition.  $\diamond$ : beer intake [B(-)],  $\square$ : shochu intake [S(-)],  $\blacklozenge$ : beer + meal intake [B(+)],  $\blacksquare$ : shochu + meal intake [S(+)].

**Figure 5. Changes in subjective drunkenness (a) and subjective drunkenness score-AUC (b) in each drinking condition.**

ethanol/water solution at the same dose of ethanol (0.3 g/kg body weight) in the fed or fasted state [14]. Our unpublished data showed that BAC in the S(-) with 5% ethanol was higher than that in the B(-) with 5% but lower than that in the S(-) with 16%. These data suggest that the difference in BAC found between the S(-) with 16% ethanol and the B(-) with 5% ethanol was not only due to the difference of ethanol concentration, but also due to the difference of the ingredients between the two alcoholic beverages [14].

The higher EDR in the B(-) than in the S(-) suggests that some ingredients in extract of beer, such as glucide and protein, increased EDR to contribute to lowering BAC. The same factor may explain why the meal increased EDR to reduce BAC. It has been shown that the intake of certain foods, such as fructose and corn peptide, increases alcohol metabolism and controls the blood ethanol and acetaldehyde levels [2]. In this study, the intake of meal decreased BAC-AUC by almost half in both beer and shochu groups (Figures 1(a) and (b)).

BAC<sub>H</sub> was higher in the S(-) than in the B(-); therefore, the influence of BAC<sub>H</sub> on the body may be stronger



L/P ratio is the ratio of lactic acid concentration to pyruvic acid concentration in the blood at 3 h after drinking. The data are expressed as means  $\pm$  SD in each drinking condition.  $\diamond$ : beer intake [B(-)],  $\square$ : shochu intake [S(-)],  $\blacklozenge$ : beer + meal intake [B(+)],  $\blacksquare$ : shochu + meal intake [S(+)]. The correlation is significant with  $r = -0.8785$  ( $p < 0.01$ , by Pearson's test).

**Figure 6. Change in lactic acid/pyruvic acid (L/P) ratio in each drinking condition (a) and correlation between L/P ratio and EDR (b).**

for shochu than for beer. Furthermore, it is suggested that a meal decreased the pharmacological and pathological influence of AcH for both alcohol beverages by reducing the level of BAC<sub>H</sub> (Figures 3(a) and (b)).

The subjective drunkenness score was as expected correlated to BAC, and also to BAC<sub>H</sub>. We confirmed that subjective drunkenness score was reduced by meal intake, corresponding to the decreases of BAC and BAC<sub>H</sub> (Figure 5(a)). The rule of thumb that "drinking when hungry makes it easier to get drunk, but drinking after food makes it harder to get drunk" was scientifically verified in this study.

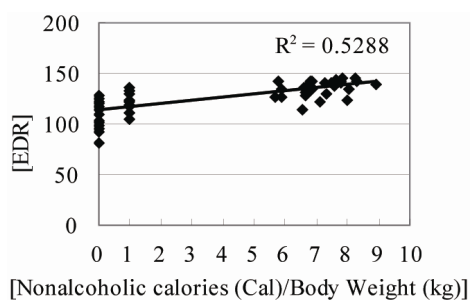
The level of serum acetic acid (SACE) showed no difference between the groups with shochu intake and beer intake, and was not decreased by the meal, which differed from BAC and BAC<sub>H</sub> (Figures 4(a) and (b)). The subjects could promptly metabolize acetaldehyde in the liver such that individual variation of the level of acetic acid was not recognized because all subjects have the *ALDH2*\*1/\*1 genotype.

These results suggest that the calories from the meal or

from the beverage promoted not only the rate of ethanol metabolism to decrease BAC but also the rate of acetaldehyde metabolism to decrease BAC<sub>H</sub>. However, the mechanism by which the meal influenced alcohol metabolism was not sufficiently clarified. As one possibility, the meal delays the transport of alcohol from the stomach to the small intestine, such that alcohol is exposed for longer as the first passing effect in the stomach [12]. Jones stated that a meal, regardless of content, decreased BAC-AUC by several mechanisms, such as the enhancement of enzyme activities involved in alcohol metabolism, NADH re-oxidation or an increase in the hepatic blood flow by dietary components [5]. Ramchandani *et al.* also considered that these kinds of mechanisms for the decrease of BAC depend on the meal [8].

In this study, the L/P ratio was increased by drinking due to the increase in NADH/NAD<sup>+</sup> during alcohol metabolism. The pyruvic acid in serum increased by a meal, which was demonstrated in the subjects who took just water with a meal (data not shown; at 1 hr after taking,  $p < 0.05$  by Dunnett's test). The EDR was in the order of B(+) > S(+) > B(-) > S(-) (**Table 1**), corresponding to the amount of calorie intake. The correlation is significant with  $r = 0.7272$  ( $p < 0.01$ , Pearson's test) (**Figure 7**). Braggins *et al.* also showed a positive correlation between L/P (NADH/NAD<sup>+</sup>) ratio and rate of ethanol oxidation in the study of rats [15]. Therefore the calorie element from a meal supplies pyruvic acid through glycolysis and increases NAD<sup>+</sup>/NADH. This increase in the ratio results in enhancement of EDR to decrease BAC and BAC-AUC. The difference of BAC and EDR between the shochu intake [S(-)] and the beer intake [B(-)] can be explained by the supplement of pyruvic acid from calorie components in the beer, which contributes to the decrease of BAC and BAC-AUC upon beer intake.

Thus, the pharmacokinetics of blood ethanol, alcohol metabolism and drunkenness are different among drinking conditions, such as different kinds of alcoholic beverages and drinking with or without a meal. Eating a meal while drinking enables more rapid recovery of the metabolic shift induced by alcohol metabolism in the liver, and depresses the rise of BAC, thereby diminishing



**Figure 7. Correlation of nonalcoholic calories with EDR.**

drunkenness. Moreover, eating a meal while drinking depresses the rise of BAC<sub>H</sub> due to an increase in acetaldehyde metabolism. Therefore, various pharmacological effects due to AcH after drinking were lowered by a meal. The choice of a beverage that includes glucide is also expected to have similar effects to some extent. Accordingly, taking calories other than ethanol while drinking is important from the viewpoint of prevention of metabolic disorders and organ damage induced by drinking.

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