# The Role of Acetaldehyde in Human Psychomotor Function: A Double-Blind Placebo-Controlled Crossover Study

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**Background:** Acetaldehyde, the first product of ethanol metabolization, is a biologically active compound, but the behavioral properties of acetaldehyde in humans are largely undefined. We investigated the acute effects of both alcohol and acetaldehyde on psychomotor functions related to automobile driving skills.

**Methods:** Twenty-four men were selected through genotyping; one-half had the ALDH2*1/*1 (active form) genotype and one-half had the ALDH2*1/*2 (inactive form) genotype. In a double-blind placebo-controlled crossover design, each subject was administered one of the following doses of alcohol: .25 g/kg, .5 g/kg, or .75 g/kg or a placebo in four trials that took place at 1-week intervals. Blood ethanol concentration (BEC) and blood acetaldehyde concentration (BAAC) were measured nine times, and psychomotor function tests (critical flicker fusion threshold, choice reaction time, compensatory tracking task, and digit symbol substitution test) were assessed seven times in total over 4 hours after study drug ingestion.

**Results:** After the consumption of alcohol, BEC was comparable in the two subject groups, whereas BAAC was significantly higher in subjects with ALDH2 *1/*2 than in those with ALDH2 *1/*1. The psychomotor performance of subjects with ALDH2*1/*2 was significantly poorer than that of subjects with ALDH2*1/*1. Significant correlations between psychomotor performance and both BEC and BAAC were observed. However, in the linear regression analysis, BAAC significantly predicted poorer psychomotor performance, whereas BEC was not associated with any measure of psychomotor function.

**Conclusions:** Acetaldehyde might be more important than alcohol in determining the effects on human psychomotor function and skills.

**Key Words:** Acetaldehyde, alcohol, aldehyde dehydrogenase, ALDH2, car driving, psychomotor function

Alcohol is metabolized into acetaldehyde in multiple organs and by several enzymes, including alcohol dehydrogenase (ADH), cytochrome P450 2E1, and catalase (1). Acetaldehyde, the first product of ethanol metabolism, is converted to acetate by the aldehyde dehydrogenase (ALDH). Mitochondrial ALDH is a polymorphic enzyme responsible for the oxidation of acetaldehyde into acetate (2). The ALDH2 gene found on chromosome 12 is the most important gene for aldehyde oxidation. It has ALDH2*1 (active form) and ALDH2*2 alleles (inactive form) (3). The latter form is found in approximately 30%–50% of Asians (4–7). The ALDH2*2 allele is associated with reduced ALDH2 activity and thus with an accumulation of acetaldehyde after alcohol intake. Therefore, those possessing this genotype are prone to ethanol-induced adverse physiological responses such as facial flushing, chest palpitations, or dysphoria after intake of even a small amount of alcohol (8), and the genotype has been found to have a substantial inhibitory effect on alcohol consumption (9,10).

Although acetaldehyde is a biologically active compound, relatively little interest has been shown in examining the effects of acetaldehyde on the central nervous system (CNS). Early studies suggested that acetaldehyde was unlikely to affect the CNS, because the blood-brain barrier (BBB) limits the diffusion of peripherally produced acetaldehyde to the brain (11,12). After alcohol consumption, peripherally produced acetaldehyde is rapidly metabolized at the BBB before penetrating the brain. However, high quantities of blood acetaldehyde are able to saturate the metabolic barrier afforded by the brain microvasculature (13). Recent studies have found that the hydrogen peroxide–catalase enzymatic pathway metabolizes ethanol into acetaldehyde within the brain (14). In addition, IP injections of acetaldehyde in both rats and mice result in a range of behavioral effects (e.g., rewarding effects, sedation, and amnesia) that are difficult to ascribe to peripheral effects (15–17). Therefore, it can be speculated that acetaldehyde plays an important role in the behavioral and psychomotor effects of alcohol. In a few studies conducted in humans, reduced slow α-wave electroencephalographic responses and an exaggerated increase in P300 latency and decrease in P300 amplitude were observed in subjects with ALDH2*1/*2 (18–20). However, the behavioral properties of acetaldehyde in humans are still largely undefined. To our knowledge, no previous study has systematically examined the relationship between psychomotor performance and blood concentrations of both alcohol and acetaldehyde after ingestion of various alcohol dosages. In this study, we investigated the acute effects of both alcohol and acetaldehyde on psychomotor functions related to automobile driving skills in healthy young men with ALDH2*1/*1 and ALDH2*1/*2 genotypes.

## Methods and Materials

### Subjects

Subjects were healthy young men, ages 19–25 years, who volunteered for the study. On screening, all subjects were

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**Table 1.** Characteristics of Subjects

| Characteristics | ALDH2*1/*1 ($n$ = 12) | ALDH2*1/*2 ($n$ = 12) | $p$ |
|---|---|---|---|
| Age, yrs | 24.4 (1.5) | 23.8 (1.5) | .296 |
| BDI, scores | 1.3 (1.4) | 3.6 (4.0) | .077 |
| Circadian Rhythm Questionnaire, scores | 34.4 (4.0) | 35.8 (2.9) | .362 |
| AUDIT, scores | 8.0 (1.3) | 6.5 (2.2) | .056 |

BDI, Beck Depression Inventory; AUDIT, Alcohol Use Disorders Identification Test.

evaluated by clinical interview, physical and laboratory examination, psychiatric assessments with a Korean version of the Minnesota Multiphasic Personality Inventory-2 (MMPI-2) (21), the Beck Depression Inventory (BDI) (22,23), and the circadian rhythm questionnaire (Korean version of the morningness–eveningness questionnaire) (24) and alcohol screening assessments including CAGE (25) and the Alcohol Use Disorders Identification Test (AUDIT) (26). Eligible subjects were required to have the intermediate type of circadian rhythm, to be within the normal range on the MMPI-2 profile, and to be within the normal range on the BDI. Subjects were excluded from the study if they had any abnormal laboratory findings and scores of over 2 on the CAGE or 11 on the AUDIT or were known to have a physical or mental disorder, to have a history of head trauma or cognitive impairment, to have taken any medications in the last 2 weeks that might interfere with daily life, to be very sensitive to alcohol, or to have a history of alcohol or other drug abuse.

## Genotyping

To evaluate the effects of alcohol on psychomotor function according to ALDH2 genotype, 12 subjects with ALDH2*1/*1 and 12 subjects with ALDH2*1/*2 were enrolled in the study. Subjects were screened by genetic polymorphism of ALDH2 (ALDH2*1 and ALDH2*2) with polymerase chain reaction—restriction fragment length polymorphism (PCR-RFLP). Briefly, the genomic DNA samples were amplified by PCR for ALDH2 locus. The PCR product was digested with a restriction enzyme of TspRI at 37°C for 3 hours, and DNA fragments were detected with an automated gel electrophoresis system.

## Procedure

This study was a double-blind, placebo-controlled crossover trial with three different doses. Each subject participated in four trials, with a 1-week interval between trials. At the beginning of a trial, each subject was administered .25 g/kg, .5 g/kg, or .75 g/kg of alcohol or a placebo. The subjects drank the test or placebo beverage in a random sequence at the four time points. Alcohol was given as a mixture of 40% (80 proof) vodka and orange juice or a placebo (orange juice). Each beverage was 300 mL and was consumed over 15 min at 5°C from an opaque bottle, through a stopper packed with vodka-soaked cotton wool, to provide olfactory masking.

The timeline for each evaluation session is shown in Table S1 in Supplement 1. Before the investigation, all subjects were thoroughly trained on all psychometric tests. Smoking and drinks or food containing caffeine were not permitted for 2 hours before the alcohol ingestion. Venous blood to measure blood ethanol concentration (BEC) and blood acetaldehyde concentration (BAAC) was drawn at baseline and four times every 15 min after study drug ingestion and nine times in total over 4 hours. Psychomotor function tests were performed at baseline and four times every 30 min after study drug ingestion and seven times in total over 4 hours.

This study was approved by Chonnam National University Hospital Institutional Review Board. The purpose and details of the study were explained to all subjects, and written informed consent was obtained.

## Determination of Ethanol and Acetaldehyde in Human Blood

Blood was carefully drawn from the median cubital vein without hemolysis. Immediately after sampling, 1 mL of blood was transferred to a 15 mL conical tube with 6 mL of ice-cold .6 mol/L perchloric acid saline-solution that had been placed in ice and deproteinized by gentle mixing. The precipitated proteins were centrifuged out at 3000 rpm for 5 min at 4°C. Five milliliters of the supernatant were moved to a closed headspace vial, and the levels of blood ethanol and acetaldehyde were instantly measured with headspace gas chromatography from PerkinElmer (Waltham, Massachusetts) with a flame ionization detector (FID), as previously described (27), with slight modifications. The headspace gas chromatography conditions for blood ethanol and acetaldehyde analysis were as follows: an

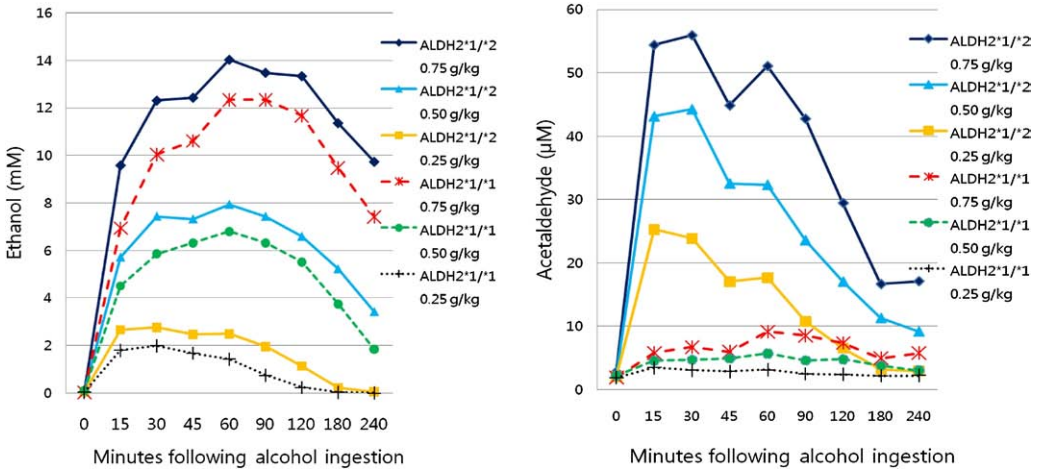


**Figure 1.** Blood ethanol and acetaldehyde concentrations in subjects according to genotype and dose of alcohol.