Relationship Between Effects of Alcohol on Psychomotor Performances and Blood Alcohol Concentrations

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ABSTRACT—Ethanol is a social drug and has been generally known to be a CNS depressant. A large fluctuation of blood alcohol concentration (BAC) is well-known to occur due to main factors such as the genetic polymorphism of the main alcohol metabolizing enzymes and the effect of blood. Few studies have substantially discussed the relationship between impaired CNS activities and BAC. In this study, focusing on the correlation of BAC, we investigated the acute effects of alcohol intake on cognitive performance in humans by objective evaluation methods consisting of the attention-demanding cognitive tasks. Tasks were administered to ten healthy male volunteers before and after ingesting established amounts of alcohol. With increased BAC, we observed prolongation of reaction time performances and lowering of a coordination performance. From the results, we concluded that cognitive performance deteriorates with an increase of BAC. Additionally, the BAC threshold that causes significant impairment of cognitive performance was estimated to be approximately 50 mg/dl (ca. 10 mM).

Keywords: Alcohol, Ethanol, Blood alcohol concentration, Cognition, Coordination

Alcohol (ethanol, ethyl alcohol) has been reported to have a depressant effect on the central nervous system (CNS). It had been utilized as an anesthetic agent before the advent of ether and barbiturates. There were many studies performed to determine the effect of acute alcohol ingestion on cognitive functions and driving performance in in vivo human studies (1–5). Previous evaluations of acute effects of alcohol on CNS performance only determined whether ingested alcohol was adsorbed from the gastrointestinal tract into the systemic circulation, although some measured blood alcohol concentration (BAC) (2, 4, 6). In those studies, the shifts of CNS performance were only discussed on the basis of dose volume of ingested alcohol, despite the BAC data.

As for the metabolism of alcohol in humans, it is well-known that alcohol is metabolized into acetaldehyde by alcohol dehydrogenase (ADH), cytochrome P450 2E1 (CYP2E1) and catalase, and then acetaldehyde is further metabolized into acetic acid by acetaldehyde dehydrogenase (ALDH) and CYP2E1. An isozyme encoded by the gene (ADH2), and ALDH2, are mainly responsible for metabolisms of alcohol and acetaldehyde, respectively, and have been known to show genetic polymorphisms, which cause different metabolic activities between individuals (7–10). Additionally, several studies report that the absorption rate and/or the amount of ingested alcohol from the gastrointestinal tract is affected by the intake of food (11–15). Even if there is consumption of identical amounts of alcohol among individuals, there would be a large fluctuation of BAC due to the reasons mentioned above. Therefore, it is assumed that the dose volume of alcohol does not always correlate with the BAC.

In this study, we examined the acute effects of alcohol consumption on in vivo human cognitive functions. We focused on the relationship between the impairments of cognitive performance and BAC; consequently, we could identify the threshold of BAC, over which the cognitive functions were affected. Cognitive performance was evaluated through objective evaluation methods consisting of attention-demanding cognitive tasks (psychological examinations) and a visuomotor coordination task.

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MATERIALS AND METHODS

Subjects
Ten healthy male volunteers, 20- to 41-year-old (average 24.3 ± 2.0), participated in this study. None of the subjects had visual or cognitive impairments, nor any history of alcohol-dependency. They were prohibited from taking any drugs and drinking alcoholic beverages the night before the experimental day. Also, they were not allowed to smoke and ingest caffeine at least 2 h before the experiments. Informed consent was obtained from all subjects prior to testing, and the study was approved by the Committee on Clinical Investigation, Tohoku University School of Medicine (the ethical committee) and was performed in accordance with the policy of the Declaration of Helsinki.

The alcohol used in this study was scotch whiskey (Suntory Old; Suntory, Osaka), including approximately 40% (v/v) ethanol. Each subject consumed alcohol at volumes of 30, 60, 90, 120 ml (12, 24, 36, 48 ml as pure ethanol volumes) and water (non-treatment), into which orange juice was added in order to conceal the smell and the dose of alcohol. They were permitted to drink at their own pace, consequently all of them finished drinking within 5 min.

Subjective sleepiness and alertness were evaluated with the Stanford Sleepiness Scale (16), a 7-point self-report measure to assess the levels of subjective sleepiness and alertness. Subjects were instructed to select the statement best reflecting their current levels of sleepiness and alertness at determined times during the experiment.

Tasks
Visual discrimination presentation tasks: A visual discrimination presentation task was adopted as an attention-demanding cognitive task. To establish a high attention-demanding condition, the visual stimuli used in this task were presented with near-visual threshold presentation time. Subjects viewed a single visual stimulus displayed on an AV tachistoscope (IS701A; Iwatsu, Tokyo), subtending 2° × 2° of visual angle. The task was to distinguish target stimuli from non-target stimuli and to promptly push the button with the right index finger when the target stimulus was presented. Target stimuli were selected from 10 kinds of digits and non-target stimuli were selected from 40 kinds of Japanese phonograms called “hiragana”. Target stimuli were presented with a probability of 20% of total stimuli. The presentation times of visual stimuli were fixed for 5, 7 and 20 ms during each session. A total of ninety single digits or letters were serially presented during the 135 s-session. To objectively evaluate the impairment by alcohol, the reaction times and the accuracy of the tasks were measured during each session. These tasks used in the present study could detect psychomotor impairments induced by a first-generation antihistamine in our previous studies (17, 18). Therefore we can compare the antihistamine-induced psychomotor impairments with the well-known alcohol-induced impairments.

Choice reaction time task (CRT) and simple reaction time task (SRT): CRT and SRT were also adopted as attention-demanding cognitive tasks. To maintain a high attentiondemanding condition, the time between a stimulus and the next was random. Subjects viewed a single visual stimulus displayed on an AV tachistoscope. The CRT was to choose a left or right stimulus against the center of the display and to promptly push the button with the left or right index finger when the corresponding-side stimulus was presented. The SRT was only to promptly push the button with the right index finger when a stimulus was presented. The stimulus was a closed circle symbol that randomly appeared at left or right against the center of the display. A total of 30 stimuli were serially presented during the session of approximately 3 min. Reaction times and an accuracy were objectively measured during each session.

Visuomotor coordination task: A personal computer program, Cube-In-A-Box (Vissuospatial I package; Psychological Software Services Inc., Indianapolis, IN, USA), was used for the visuomotor coordination task based on a visual stimulus. The program presented an open large square that randomly moved about the display for about 1 min. A closed small square was also present on the display, but its movement was under the control of a subject via the manipulation of the mouse. The task was to keep the small square within the boundaries of the large square. Since the large square was continuously re-positioned by the computer, the subject had to constantly readjust the position of the small square. The score of the task was based on the length (%) of time the subject was able to maintain the position of the small square within the large square. The mean value of 4 successive trials of the visuomotor coordination task was used as the coordination score for each session.

Study design
Figure 1 shows a brief time schedule for this study. Each subject randomly ingested four doses of alcohol or water on different days at intervals of at least 3 days. With each subject, three kinds of the aforementioned attention-demanding cognitive tasks were given before and 30 min after consuming alcohol. One reason why the task performance was re-evaluated 30 min after the ingestion was that BAC reaches its maximum level at 30 – 90 min after an oral administration in humans (11, 12, 19 – 21). One more reason is that it takes about 30 min to conduct the three kinds of tasks. Prior to each task, subjects were given time to practice. Subjects were instructed to take 2-min rests between each session so that they could keep a high level of attention during the performance of the tasks. Blood sam-
Fig. 1. Brief time schedule of the experiment, which was started at 11 a.m.—12 p.m.

Examples were taken from subjects at the end of the tasks (approximately 60 min after the ingestion of alcohol), when BAC might reach the maximum.

Analysis of BAC

BACs were evaluated by gas chromatography. An aliquot of blood sample was applied to the gas chromatograph. The standard curve from 0.3 to 400 mg/dl was used. The analysis was performed on a type GC-15A gas chromatograph (Shimadzu, Kyoto) equipped with a hydrogen flame ionization detector (FID, Shimadzu). The column used in this analysis was Porapak-Q 80/100 (1000-mm-long, 3-mm I.D.; Waters, Milford, MA, USA) made of glass. The temperature for the injection, the column and the detector were 200°C, 135°C and 200°C, respectively; and nitrogen gas was used as a carrier gas at a flow rate of 60 ml/min. A BAC of less than 0.3 mg/dl was regarded as 0 mg/dl.

Data analyses

Absolute values of reaction time, accuracy and coordination score differed, even when their tasks were conducted under identical conditions, between inter-individuals and/or inter-days. Ratios of after/before the ingestion of alcohol were used as task performances. Values are represented as mean ± S.E.M. Multiple comparisons were conducted by administering one-way analysis of variance (ANOVA) and the Dunnett's comparison test was adopted as a post-hoc analysis against the non-treatment (0 ml) group. The relationship between BAC and the task performances was evaluated by using the Pearson's correlation. The statistical significance for each analysis was defined as P<0.05.

RESULTS

Subjective sleepiness and alertness

Time courses of the subjective sleepiness and alertness are shown in Fig. 2. Immediately after starting the task,
the level of sleepiness and alertness tended to increase. The level in the non-treatment group tended to be not significantly lower than any of the other groups during the tasks and those in other groups were almost the same degree.

Tasks

**Task performances in a non-alcohol condition:** Absolute values of reaction time and accuracy on five kinds of attention-demanding cognitive tasks before the ingestion of alcohol (subjects were sober) are shown in Fig. 3. The reaction times in three kinds of tasks of 5, 7 and 20 ms-presentation time were 476 ± 8.71 (mean ± S.E.M.), 440 ± 8.21 and 396 ± 5.00 ms, and the accuracies were 0.680 ± 0.043, 0.869 ± 0.030 and 0.968 ± 0.008, respectively. The shorter the presentation times were, the longer the reaction time and the lower the accuracy became. The reaction times in the CRT and the SRT were 293 ± 3.61 and 263 ± 4.15 ms, respectively, and the accuracy in the CRT was 0.988 ± 0.002. The reaction time in the CRT was longer than that in the SRT. This may be because the CRT required one more process, left and right-discrimination, than the SRT. Furthermore, since the three tasks of 5, 7 and 20 ms-presentation time had a more difficult process than the CRT, which is digit and letter-discriminative, and presented digits or letters with near-visual-threshold presentation time, task performance in these three tasks were thought to be lower than those in the CRT and the SRT.

**Visual discrimination presentation tasks:** The ratios of the reaction time and accuracy are shown in Fig. 4. The reaction times in the three kinds of tasks of 5, 7 and 20 ms-presentation time were prolonged along with dose (Fig. 4a). For the task of 5 ms-presentation time, the reaction time in the 120-ml dose group was significantly prolonged when compared to that in the non-treatment group (P<0.05). For the tasks of 7 and 20 ms-presentation time, the reaction times in the 90-ml and 120-ml dose groups were significantly longer than that of the non-treatment group (7 ms: P<0.01, P<0.001; 20 ms: P<0.01, P<0.05; respectively).

On the other hand, the accuracy of the three tasks were not significantly reduced when compared to those of the non-treatment group, although the accuracy of the tasks of 5 and 7 ms-presentation time tended to decrease along with dose (Fig. 4b).

**CRT and SRT:** The reaction times of the CRT and the SRT are shown in Fig. 5a. In the CRT and SRT, the reaction times were dependent on dose, and the reaction times in the 90-ml and 120-ml dose groups were significantly longer than that of the non-treatment group (CRT: P<0.05, P<0.01; SRT: P<0.05, P<0.05, respectively). However, the accuracy of CRT tended to decrease in the 90-ml and 120-ml dose groups (data not shown).

**Visuomotor coordination task:** The visuomotor coordination score is illustrated in Fig. 5b. The coordination score declined as the dose increased. This resulted in the scores in the 90-ml and 120-ml dose groups that were significantly different from that of the non-treatment group (P<0.05, P<0.01, respectively).

**Relationship between BAC and task performances**

BAC of each study about 60 min after the ingestion of alcohol is plotted against its dose volume (Fig. 6). The mean concentration at each dose normally increased with an increase of dose. The individual concentrations, especially at higher dose volumes, overlapped between dose volumes. This phenomenon was probably due to the inter-individual differences of enzyme activities of ADH and/or ALDH.

In order to clarify the relationship between the impaired performance and the BAC, individual performance data in each task are plotted against their respective BAC in Figs. 4c, 5c and 5d. The reaction time ratios in the visual discrimination presentation tasks with 5, 7 and 20 ms-presentation time (Fig. 4c), as well as CRT and SRT (Fig. 5c), prolonged significantly along with the increase of BAC (5 ms: P<0.001, 7 ms: P<0.001, 20 ms: P<0.001, CRT: P<0.001 and SRT: P<0.01). However, the accuracy ratios did not show any correlation with BAC (data not shown). In the visuomotor coordination task (Fig. 5d), the score ratio decreased with the increase of BAC (P<0.001).

**DISCUSSION**

This single-blind and cross-over study clearly suggested that alcohol causes the impaired cognitive performance. After the oral administration of alcohol to ten normal male volunteers, the impaired cognitive performances were objectively evaluated by visual discrimination presentation.
Fig. 4. Task performances of reaction time (a, c) or accuracy (b) on the visual discrimination presentation tasks with 5, 7 and 20 ms-presentation time, based on alcohol doses or BAC. Y-axes show the ratios of the reaction time and the accuracy after/before the ingestion of alcohol. a and b: *P<0.05, **P<0.01, ***P<0.001 vs the non-treatment group (0 ml) by Dunnett's multiple comparison test (n = 10 in each dose group); c: The relationships were analyzed by Pearson's correlation test (n = 50).

tasks, CRT and SRT, using an AV tachistoscope. A visuomotor coordination task using a personal computer program was also conducted. Although the increase in subjective feelings of sleepiness and alertness was not significant in relation to alcohol dose, the objective evaluations showed that the reaction times were prolonged and the coordination score was decreased along with the increase of BAC. Concerning the accuracy, however, no significant shift was observed. Thus, the present study showed that alcohol causes the prolongation of the reaction time and/or the decision time, but not the deterioration of the decision itself. Although the cognitive performance was linearly deteriorating (Figs. 4c, 5c and 5d), we estimated that the threshold of BAC, over which the CNS cognitive functions are impaired, was 50 mg/dl (ca. 10 mM), because it was observed that the cognitive performance became significantly impaired at an alcohol dose of more than 90 ml (Figs. 4a, 5a and 5b), a dose over the minimum BAC of about 50 mg/dl (Fig. 6).

Impaired psychomotor performances are common adverse effects of alcohol. Drug-induced psychomotor impairments can also interfere with the daily activities that require full alertness. Impaired performance caused by alcohol and drugs could potentially be dangerous for people who drive, pilot aircraft or operate machinery. We used the same attention-demanding cognitive tasks to evaluate antihistamine-induced cognitive decline (17). Cognitive performance in the attention-demanding task significantly deteriorated after the intravenous treatment with 2 mg of d-chlorpheniramine. The results of our studies clearly re-
revealed that psychomotor performances could be similarly impaired at the therapeutic doses of antihistamines and at the BAC of over 50 mg/dl. We recently visualized the neural correlates of antihistamine-induced cognitive impairments in humans using [15O]H2O and positron emission tomography (PET) (18). The sedative effects of older antihistamines at therapeutic dose levels are known to enhance the CNS effects of ethanol in producing more performance decrement than the simple additive effects (22). It could be also important to evaluate the enhanced cognitive impairments caused by antihistamine plus ethanol using [15O]H2O and PET.

In this study, five different amounts of alcohol were given to subjects. However, the individual BAC data overlapped between dose volumes, especially at the higher volumes (Fig. 6). This large fluctuations of BACs are generated by metabolizing activities of alcohol dehydrogenase and acetaldehyde dehydrogenase, the main metabolizing enzymes of ethanol and acetaldehyde, respectively. These enzymes are generally known to show genetic polymorphisms in humans, resulting in differing metabolic activities between individuals. Another factor is the extent of absorption rate. The amount of alcohol absorbed from the gastrointestinal tract, mainly the duodenal and jejunal tracts, is influenced by the gastric emptying rate, which varies by the intake of food and/or drugs. In addition, the inter-individual differences of BAC might be caused by an effect of the dose volume of alcohol which was not adjusted to the body weight of each subject. In our results, significant changes of cognitive performance based on dose volumes were observed; however, the performance based
on BACs were more clearly observed to deteriorate along with the increase of BAC.

From this study we concluded that a BAC of over 50 mg/dl significantly impairs cognitive functions. The actions of alcohol in the brain have been extensively studied over the last several decades. Alcohol was initially thought to impair the CNS functions in a non-specific manner by altering membrane fluidity. Recently, however, it has been pointed out that alcohol instead acts on specific neurotransmitters and their receptors (23–25). Therefore, alcohol has been reported to affect a variety of different neurotransmitters such as monoamines (26–29), neuropeptides, adenosine (30, 31), glycine (32, 33) and acetylcholine (34, 35).

Recently, several reports have been published on the interactions of both acute and chronic alcohol treatments with two major amino acid transmitters, GABA and glutamate (23–25). GABA is a major inhibitory neurotransmitter in the brain, and the activity of its GABAA receptors is facilitated by acute alcohol ingestion. The NMDA receptor, one of the glutamate receptors that plays an important role of an excitatory amino acid transmission, has also been known to be inhibited by acute alcohol ingestion. Both GABAA and NMDA receptors have been shown to be affected at alcohol concentration ranges of more than 5–10 mM (ca. 25–50 mg/dl) (36–38). After the absorption of alcohol from the gastrointestinal tract, it is rapidly distributed throughout all the tissues (39). Therefore, the concentration in the brain is ordinarily parallel with BAC. The threshold of 50 mg/ml (ca. 10 mM) obtained from this study is compatible with the concentration range in which both the activation of GABAA receptors and the inactivation of NMDA receptors have occurred (24). This study further supports that impaired cognitive functions after an acute intake of alcohol are mainly responsible for the effects of alcohol on both GABAA and NMDA receptors.

In the cerebellum, the effects of alcohol have been investigated by many researchers. Chu (40) reported that alcohol caused motor incoordination, which was correlated with the changes in rat cerebellar Purkinje cell activity. Alcohol-induced motor incoordination was directly, indirectly and/or partially related to GABAergic mechanism in the cerebellum in animal studies (41–45). In humans, many kinds of cerebellar diseases or injuries are well-known causes of ataxia, asynergy, dysdiadochokinesia, etc., which are strongly related to coordination performance. The eye-hand coordination task has been reported to activate the cerebellar areas related to movements of the eye and hand (46). The visuomotor coordination task used in this study depended on the function of cerebellar motor coordination; therefore, it is also suggested that more than 50 mg/dl of BAC (ca. 10 mM) impairs motor coordination function in humans.

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