Acute Effects of Alcohol on Cognitive Function and Central Nervous System Assessed by Auditory Event-Related Potentials

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Introduction

Alcohols are widely used as cleaning agents, thinners and for drinking. They are also known to be potent central nervous system depressants and irritants\textsuperscript{1-3}; for that reason, it might be difficult to distinguish the influence on the central nervous system function of alcohol from that of other chemical agents, in particular, among solvent-workers. International review bodies have recommended that increased research be directed toward objective evaluation of central nervous system dysfunctions in persons exposed to organic solvents including alcohols\textsuperscript{4,5}).

The effects of alcohol on latencies of cerebral evoked potentials (EP) originating from the peripheral level of the sensory system remain less clear, although EP amplitudes tend to be depressed\textsuperscript{6,7}). Jensen and Krogh observed a significant prolongation in the P200 latency of visual evoked potentials (VEP) after alcohol intake while the N75, P100 and N145 latencies of VEP did not change\textsuperscript{8}); in addition, a significant dose-response relationship between ethanol dose and the P300 component of the event-related potential (ERP) has been reported by some study groups\textsuperscript{9-12}). On the other hand, Skalka et al failed to find significant changes in latencies of the VEP after alcohol ingestion\textsuperscript{13}). Apart from electrophysiological studies, Matsunaga and Mukasa reported that alcohol affected neuropsychological functions such as memory and attention\textsuperscript{14}). On the basis of these findings, the EPs with a long latency reflecting higher nervous system functions would be expected to be more sensitive for detection of acute effects of alcohol than those with a relatively short latency.

The EP or ERP technique offers a profitable approach for assessing the level of brain functioning as it permits the concurrent investigation of electrophysiology and cognition. In particular, ERPs can be obtained in conjunction with behavior, or even when no behavioral response is required; they can be recorded for both attended and unattended stimuli\textsuperscript{15}). Thus, the ERP method is considered to be a very sensitive index of the functional integrity of the brain. In the present study, six latencies of the auditory ERP were determined in healthy volunteers to clarify which sites of the central nervous system are influenced by acute administration of alcohol at an early stage.

Materials and Methods

1. Subjects

The subjects consisted of 13 healthy male medical students, aged 20 to 26 (mean 23) years; they consented readily to become volunteers for this study. All these subjects had a history of alcohol-induced facial flushing. They drank alcohol equivalent to 0-450 (mean 100) ml of 100% ethanol per week. They were not occupationally exposed to neurotoxic substances such as lead or organic solvents, and had never suffered from neurologic, psychiatric or endocrinological disorders. None of them took drugs, alcohol, cigarettes or other beverages containing caffeine in the afternoon of the examination day.

2. Study design

ERP testing was conducted by ingesting 200 ml of Japanese spirits (containing 25% ethanol) at 4:50-5:00 p.m.; latencies were measured in the same subject at 4:30-4:45 p.m., at 6:00-6:15 p.m. and at 7:00-7:15 p.m. (i.e., before and 1-hr and 2-hr after ethanol ingestion), for a total of three times on the same day. In addition, the ERP testing was done again in the same manner by ingesting
200 ml of water on another day for reference to circadian rhythm within the same time period, 4:30-7:00 p.m.

3. Electrophysiological study

The auditory ERP was measured by the use of a Medelec MS-92 two channel electromyograph, Medelec ST-10 stimulator and Apple IIe microcomputer in an electrically shielded room. Measurement of the ERP was conducted using a method with the target-selection (i.e., odd-ball) paradigm. The subject was presented with a random sequence of two distinguishable stimuli; 80 percent of 300 tone bursts of 20 msec duration (rise/fall time, 6 msec) had a frequency of 1000 Hz (non-target tone stimuli) and 20 percent had a frequency of 2000 Hz (target tone stimuli). These stimuli were delivered binaurally via earphones at an intensity of 90 dB SPL and a rate of 1 tone burst every 2 sec. The subject was instructed to count only the target tone mentally. In all cases, the reported total of the target stimuli was correct within 3 stimuli of the actual total presented. Cerebral responses to the two stimuli were recorded at the vertex (Cz) of a 10-20 system and the linked mastoids, and averaged separately (bandpass, 2-100 Hz); then the negative (N100) - positive (P165) - negative (N200) - positive (P300) complex elicited by the target tone and the negative (N100) - positive (P200) complex by the non-target tone were recorded as shown in Fig. 1. The daily variations (coefficients of variation) in these latencies in a 32-year-old male subject for 14 days were between 3.2% and 5.8%.

The ERP components are considered to be as follows: among components elicited by the target tone, the N100 is enhanced when attention is directed to the sensory channel in which the stimulus occurs. The P165 and N200 are associated with processes that underlie signal identification and response selection. The P300 component is elicited only in circumstances where the subject is required to distinguish one stimulus (target tone) from a group of other stimuli (non-target tone). The P300 latency corresponds to the evaluation time of target stimuli; when the task is difficult, the latency becomes longer. Thus, P300 seems to reflect cognitive function in humans; the functional significance of P300 and other ERP measures is generally inferred from the behavioral data since the physiological substrate of "cognitive" potentials is unknown. On the other hand, the response to the non-target tone consists of a series of waves (i.e., N100 and P200) that relate to an auditory stimulus.

4. Statistical Analysis

The Bonferroni multiple comparison method was used to determine the significance levels of repeated measurements in latencies of the ERP on the same day, and of matched differences between tests conducted at the same time on two different days. The relationships between the change in each latency and dose of ethanol per body weight were tested by Pearson's product moment correlation coefficient. All analyses were performed using the Statistical Packages for the Biosciences (SPBS, Uni-Science Co.).
Results

Table 1 shows ERP latencies before and after ingestion of alcohol and water in 13 male subjects. The latency of P300 elicited by the target tone at 1-hr and 2-hr after alcohol ingestion was significantly longer than that prior to alcohol ingestion, and than the latency measured at the same time on another day when water was administered to the subjects. The N200 latency at 2-hr after alcohol ingestion was also significantly prolonged as compared with that before drinking alcohol. The change in P300 latency observed between before and 2-hr after alcohol ingestion was significantly correlated with the dose of ethanol per body weight in the 13 subjects (Fig. 2), while no change in other latencies was correlated (p>0.05).

Discussion

The major results in this study were that P300 latency, as well as N200 latency, were significantly prolonged in subjects with alcohol-induced facial flushing after ethanol ingestion of 0.54-0.74 g/kg body weight (BW); the change in P300 latency was significantly correlated with ethanol dose per BW. Therefore, it is suggested that P300 latency is the most sensitive indicator for assessing acute ethanol effects among ERP components with latencies between 100 and 500 msec.

Maximally prolonged latencies of P300 and N200 were found at 2-hr after drinking stopped in the present study; while, blood ethanol concentration and the change in heart rate variability have been reported to reach peaks at 30-60 min8,19 and at 30-90 min20) after intake, respectively. The effect of ethanol on P300 latency related to cognition of higher nervous functions, agrees with the results of other investigations8,10-12). Acute ethanol intoxication also causes impairment in storage of extremely

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<th>Table 1 Latencies of auditory event-related potentials (mean ± SD, msec) before and 1-hr and 2-hr after alcohol or water ingestion in 13 male subjects</th>
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a,b,p<0.05 and c,d,e p<0.01 (the Bonferroni multiple comparison method was used to determine the significance levels of repeated measurements on the same day, and of matched differences between tests conducted at the same time on two different days).
Fig. 2 Relationship between 2-hr alteration in the P300 latency due to alcohol ingestion and dose of ethanol per body weight in 13 male subjects. 

r indicates Pearson's product moment correlation coefficient.

short-term memory process in Benton's visual retention test\textsuperscript{14}). On the other hand, Genkina observed that the amplitude of the P300 wave decreased significantly after ingestion of an ethanol dose of 0.82 g/kg BW despite the absence of any significant change in an ethanol concentration of 0.41 g/kg BW by means of the visual ERP\textsuperscript{9}). Also, Teo and Ferguson indicated that prolongation of P300 latency with increased ethanol doses was in a dose-dependent manner\textsuperscript{10}, as shown in Fig. 2. Thus, it is concluded that ethanol, in proportion to its dose, affects the higher nervous functions, including cognition, at a relatively early stage.

No ethanol-induced prolongation in latencies of less than 200 msec was seen in the current study. A similar finding has been reported by three previous studies\textsuperscript{8, 13, 21}, in which VEP latencies of more than 180 msec were significantly prolonged but no slowing of latencies below 180 msec could be found (the ethanol doses were between 0.7 and 1.2 g/kg BW). The VEP latencies, elicited by flash stimuli, of 140 msec and above increased after ethanol administration of 1 g/kg BW level\textsuperscript{22}). On the other hand, the brainstem auditory evoked potential (BAEP) with a latency of less than only 10 msec is well-known to be resistant to changes in attention or consciousness and to pharmacologic insults\textsuperscript{23}); whereas, some “peak” latencies of the BAEP were significantly prolonged after ethanol intake of 1 g/kg BW (the authors did not test the statistical significance of the changes in their “interpeak” latencies)\textsuperscript{24}). In this way, the relatively short-latency EPs appear to be less affected by ethanol; such EPs might also respond to higher doses as it is likely that all brain loci are ultimately affected by ethanol.

Teo and Ferguson, however, found a significant prolongation in the N100, P165, N200 and P300 latencies of ERP after ethanol intake of 0.54 g/kg BW\textsuperscript{10}, which is not consistent with our results in regard to the dose and influenced peaks. Two explanations are possible for this disagreement: (1) When ethanol was administered to the subjects, Teo and Ferguson adulterated it with orange juice and we did so only with water. For that reason, the absorption rate of ethanol in the stomach and small intestine might have been different between these two groups. (2) About 50–60% of Orientals exhibit ethanol-induced facial flushing, but only a few percent do so among Caucasians\textsuperscript{25}). It has also been reported that flushers are deficient in aldehyde dehydrogenase I, which has a low Km value for acetaldehyde\textsuperscript{26}); nevertheless, the alteration of blood ethanol concentration in flushers was similar to that in non-flushers\textsuperscript{19}). Accordingly, the above discord may be attributable to the difference in race and genetic predisposition between Japanese and Australian subjects.

Cellulotoxic studies do not yet offer a comprehensive and consistent interpretation of the effects of ethanol on electrophysiological processes in single neurons or integrated circuits. There have been two hypotheses concerning ethanol toxicity: (1) the major effects of ethanol are on synaptic transmission
and are cumulative in polysynaptic paths\(^3,27\) and (2) the mechanism of action probably involves interference with ion transport at the cell membrane rather than at synapses\(^1\). The VEP latency has been considered to be a sensitive indicator of both long- and short-term exposure such as visual fatigue induced by visual display terminal work\(^28\). Thus, latencies of VEP or P300 may be easily affected by changes in the arousal or cognitive function of the cortex due to visual fatigue or ethanol, inasmuch as these latencies have many synaptic circuits in the long pathway between the periphery and cortex. In contrast, latencies of the short-latency somatosensory evoked potentials or BAEP may be resistant to acute effects of ethanol, since they have at most a few synapses. Further study will be required to establish the cellulo-physiological mechanism in alcoholic neurotoxicity.

Finally, long-term brain impairment in chronic alcoholics also has been observed by Ciesielski et al\(^29\), who suggested that cognitive brain potentials (N200 and P300) were more sensitive indicators of cerebral impairment than psychometric data. Thus, alcohol is considered to be one of the most important confounders for ERP testing. When long-latency EPs, including ERPs, are measured to evaluate subclinical effects of environmental neurotoxins such as organic solvents, particular attention should be paid to not only the degree of the daily drinking habit (i.e., its dose, frequency and duration) but also the interval between the measurement and alcohol intake, together with other confounders (e.g., age)\(^16\), to preserve the comparability of the ERP data between exposed and unexposed groups.

**Summary**

To clarify which sites of the central nervous system are influenced by acute administration of alcohol at an early stage, auditory event-related potentials (ERP) using a target-selection paradigm were measured in 13 healthy volunteers. In the recorded waveforms of ERPs, the N100, P165, N200 and P300 latencies for the target tone and the N100 and P200 latencies for the non-target tone were determined in each subject before and 1- and 2-hr after ingestion of 200 ml of alcohol (containing 25% ethanol) or of 200 ml of water, for a total of six times on two different days. The P300 latency was significantly prolonged at 1- and 2-hr after alcohol ingestion; and, the N200 latency was significantly prolonged at 2-hr after alcohol ingestion. The 2-hr alteration in the P300 latency after alcohol ingestion was positively correlated with the ethanol dose per body weight. These data suggest that ethanol, in proportion to its dose, affects cognitive function estimated by the P300 latency earlier than other lower central nervous system functions. Evaluating subclinical effects on central nervous function, using the ERPs, of environmental neurotoxins such as organic solvents, researchers should pay particular attention not only to the degree of the drinking habit but also to the interval between the measurement and alcohol intake.

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**References**


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