Acute Effects of Alcohol on Auditory Brainstem Potentials in Humans

Abstract. *Auditory brainstem potentials were recorded from human subjects before and after an intoxicating dose of alcohol. Following alcohol ingestion there were significant, progressive increases in the latencies of brainstem potential peaks III through VII. No changes in peak amplitudes were found. The results indicate that alcohol has a depressive effect on neural transmission within the primary auditory brainstem pathway.*

Sensory evoked potentials have been used to study the effects of alcohol on the human central nervous system. Significant reductions in the amplitude of auditory cortical potentials are normally reported after alcohol ingestion (*1*). Cortical potentials elicited by visual and somatosensory stimulation have also been reported to be reduced in amplitude, although those components of the potentials which were thought to originate in the primary receiving areas in each modality remained unchanged (*2*).

Similar results have been noted with animal subjects. Cortical potentials are generally depressed by alcohol while the amplitudes of potentials recorded from subcortical structures are unaffected (*3, 4*), one exception being auditory potentials from the inferior colliculus which are reduced in amplitude (*4*).

To date no studies have been conducted to examine in humans the effects of alcohol on subcortical structures involved in sensory transmission. However, techniques have been developed for recording auditory brainstem potentials from the scalp in humans. These potentials are the presumed "far-field" reflection of neural events occurring in the primary auditory pathway (*5*), and consist of a series of seven positive waves of submicrovolt amplitude within the first 10 msec after a click stimulus. The first peak in the waveform probably represents the compound action potential of the auditory nerve, and the remaining peaks have been attributed to subsequent activity in the cochlear nucleus, superior olive, lateral lemniscus, and inferior colliculus (*6–8*). By recording auditory brainstem potentials in rats, we have demonstrated that acute alcohol intoxication produces significant and progressive prolongations of the latencies of brainstem potential peaks; these results indicate a depressive effect of alcohol on sensory transmission within the primary auditory pathway (*9*). In the study reported here, the analogous experiment was conducted with human subjects. Recordings were also made of the midlatency potentials (latencies between 10 and 50 msec) which are attributed to thalamic or early cortical activity (*8*).

The subjects were six adult males, including the three authors and three laboratory personnel. All had a history of social drinking but not of alcohol abuse. They were neurologically intact and had normal hearing. Testing was conducted in the afternoon after the subjects had fasted since breakfast. Alcohol dosages were selected for each subject according to his capacity for alcohol as judged from the frequency and amount of alcohol normally used. The aim was to achieve a uniform stage of clinical intoxication for all subjects. The resulting dosages of alcohol ranged from 0.55 to 1.65 ml per kilogram of body weight, and were given in the form of commercially available vodka mixed with orange juice to a concentration of 20 percent (by volume). The subjects consumed the drinks at their own rate within a maximum time limit of 30 minutes. During testing the subjects reclined on a bed situated in a sound-attentuating chamber. Monaural auditory stimuli consisting of 0.5-msec clicks were presented through earphones at a rate of 10 per second. Each ear was tested. Two stimulus intensities were used, 75 and 55 dB above the threshold for normal hearing. Electrodes were attached at the vertex and mastoids, with the ipsilateral mastoid serving as the reference electrode and the contralateral mastoid the ground. The brain electrical activity was amplified by a factor of 10^5 with a bandpass of 100 to 3 kHz. Averaged potentials were summed over 2048 click presentations for 10.48 msec following click onset. When midlatency potentials were recorded the averaging epoch was extended to 51.2 msec, with an amplification bandpass of 7 to 500 Hz. Replicated waveforms were collected in all conditions. Before administration of alcohol, recordings were taken for 1 hour in a normal condition. After the alcohol was consumed, recordings were taken at regular intervals for up to 2 hours. Blood samples were taken from each subject 1 hour after alcohol ingestion and after the completion of testing.

All subjects reached a level of moderate intoxication as indicated by slight slurring of speech, dizziness, slight ataxia, and joviality. Analysis of blood samples indicated alcohol levels of 44 to 147 mg/100 ml (*10*), although the clinical effect of the alcohol was similar across the subjects.

The brainstem potentials for one subject for the 75-dB stimulus taken before and 95 minutes after the start of the alcohol consumption are shown in Fig. 1. The seven peaks (labeled I to VII) are clearly distinguishable, as they were for all subjects, and fall within the normal latency limits for the stimulus intensity (*7, 11*). However, after alcohol ingestion the peaks were shifted to longer latencies

Table 1. Latencies of auditory brainstem potential peaks before and after alcohol consumption. The statistical significance of the change in each peak latency is given; N.S., not significant.

Subject	Latency of peak (milliseconds after stimulus onset)						
	I	II	III	IV	V	VI	VII
				Before alcohol			
1	1.68	2.97	3.85	5.10	5.80	7.58	9.18
2	1.50	2.83	3.81	5.18	5.88	7.35	9.05
3	1.49	2.82	3.60	4.84	5.38	6.93	8.37
4	1.81	2.70	3.68	4.90	5.40	7.05	8.57
5	1.77	2.82	3.78	5.04	5.90	7.20	8.54
6	1.40	2.73	3.83	5.11	5.71	7.54	9.14
Mean	1.61	2.83	3.78	5.05	5.70	7.29	8.83
				After alcohol			
1	1.65	2.97	3.82	5.13	5.90	7.68	9.25
2	1.47	2.78	3.95	5.40	6.05	7.60	9.25
3	1.53	2.92	3.80	5.13	5.64	7.21	8.88
4	1.82	3.03	3.87	5.14	5.58	7.21	8.86
5	1.80	2.87	3.88	5.16	6.05	7.28	9.06
6	1.44	2.82	3.94	5.31	5.87	7.77	9.33
Mean	1.62	2.90	3.88	5.21	5.85	7.46	9.10
				Change			
	0.01	0.07	0.10	0.16	0.15	0.17	0.27
				P			
	N.S.	N.S.	<.05	<.01	<.001	<.01	<.01

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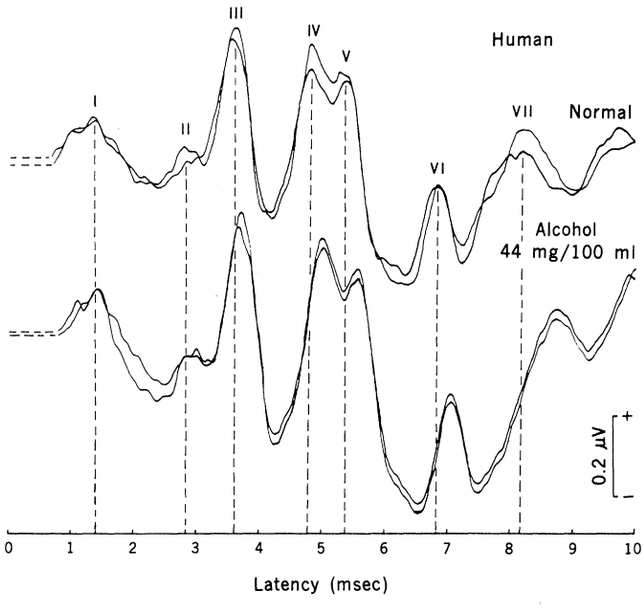

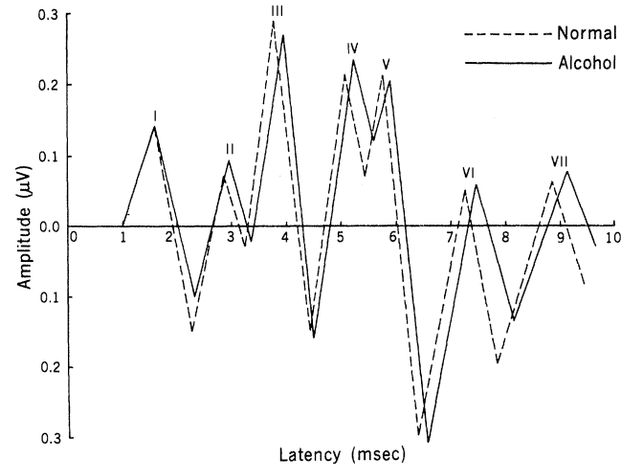

Fig. 1 (left). Auditory brainstem potentials for one subject before and after consumption of an intoxicating dose of alcohol. Replicated waveforms are shown for each condition. Seven positive peaks (I to VII) were identified; their latencies before alcohol consumption are indicated by dashed vertical lines. The acoustic stimulus was a 75-dB, 0.5-msec click presented at a rate of 10 per second. Recording was initiated at stimulus onset. Positive voltage at the vertex referred to the ipsilateral mastoid is plotted upward. Each waveform is the average of data for 2048 stimulus presentations. Fig. 2 (right). Schematic auditory brainstem potential waveforms showing the mean amplitudes and latencies across the six subjects for the 75-dB stimulus; dashed line, before alcohol; solid line, after alcohol.

compared to those in the control condition, particularly the later peaks. The cumulative increase in peak latencies was seen for every subject (Table 1).

The mean amplitudes and latencies for the 75-dB waveform peaks and troughs are shown in schematic form in Fig. 2. Although the data for each ear in each subject were analyzed separately, no differences were seen; consequently the mean data for both ears are presented.

Several conclusions are clear from Fig. 2. (i) Alcohol had no effect on the latency of peak I, and thus presumably had no effect on auditory nerve activity. (ii) There was a progressive increase in the latency of peaks II through VII as shown in Table 1. (iii) Alcohol had no significant effect on the amplitude of any of the potentials.

Similar effects were found for the lower (55-dB) stimulus intensity. Only the latencies for peaks III and V could be reliably determined at that intensity, however. The latency shifts due to alcohol for peaks III and V at 55 dB were 0.11 msec ($P < .1$) and 0.10 msec ($P < .01$), respectively. Again, there were no changes in peak amplitudes.

Although the effect of alcohol ingestion on the brainstem potentials was highly reproducible in all six subjects, the absolute latencies of the peaks, even after alcohol, were within the range of normal variation (*7, 11*). It remains to be seen whether at higher doses the effect would be proportionately greater. Thus, even though this procedure is sensitive to small changes in peak latency, it is essential that brainstem potentials be recorded in a normal condition before conclusions regarding the effect of alcohol can be made for an individual subject.

The analysis of the midlatency potentials was confined to the negative (N_a) and positive (P_a) peaks with mean latencies of 18.9 and 29.4 msec, respectively. The latency of P_a was increased by 1.3 msec after alcohol ingestion ($P < .05$), while no change was seen for the latency of N_a. There was no significant change in the amplitude measured between N_a and P_a.

In order to ensure that these effects of alcohol on auditory brainstem potentials were due to the alcohol and not to the time spent by each subject in the testing sequence, two subjects were retested over a 2-hour period without ingesting alcohol. No significant changes in peak latency were found.

The results of this study demonstrate that alcohol has a depressive effect on neural transmission within the primary auditory pathway in humans. Previous studies have indicated that auditory brainstem potentials are highly resistant to alterations in the state of the organism including arousal, sleep, and even metabolic coma (*7, 12, 13*). Since the prolongation of peak latency was seen at an early stage of sensory transmission (peak III), the effect of alcohol presumably occurs as peripherally as the relay nuclei in the medulla, such as the cochlear nucleus or superior olive. These results are consistent with those found in rats (*9*) and cats (*14*). It is not surprising that alcohol affects brainstem structures, since signs of brainstem dysfunction such as dizziness, unsteady gait, and nystagmus are prominent in both acute and chronic alcohol intoxication.

The latency increases found here followed closely the clinical signs of alcohol intoxication. For instance, the clinical state and magnitude of the latency shifts were consistent across the six subjects even though the blood alcohol levels required for intoxication were different for each subject. The smallest effect, in fact, was found for a subject whose blood alcohol level was 102 mg/100 ml, while one of the larger effects was found for a subject with blood alcohol concentration of only 44 mg/100 ml (Fig. 1), which is well below the usual level for legal intoxication. It is possible, therefore, that the changes in the brainstem potentials more accurately correlate with the effect of alcohol on the nervous system than do blood alcohol levels.

Also, the time course for development of the alcohol effect on auditory brainstem potentials went pari passu with that of intoxication. Although the time course was not studied systematically, there was a progressive change in which later peaks (V to VII) were first affected by alcohol, usually within the first half-hour after onset of drinking, followed by changes in the earlier peaks (III and IV). This roughly paralleled the subjects' verbal reports of maximal intoxication, which usually occurred 45 to 60 minutes from the onset of drinking.

The sites of action of alcohol are not

clear from this study. Presumably all except the lowest levels of auditory transmission in the brainstem were affected because the increase in latency was seen for all peaks except I and II. However, most of the latency increase occurred between peaks III and IV and between peaks VI and VII; this suggests that the intervening processes between those peaks were most susceptible to alcohol.

Alcohol intoxication produces definite and consistent changes in the early auditory evoked potentials from the human brainstem. The value of this observation lies not only in the information it provides concerning the neurological effects of alcohol, but also in the possibility for a functional dissection of brainstem connections in an intact subject. Systematic correlations of the effects of different drugs, with known effects on different central pathways, on the brainstem potentials offers a means of identifying specific transmission or conduction dysfunction.

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References and Notes

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14. K. Squires, N.-S. Chu, A. Starr, *Proceedings, San Diego Biomedical Symposium, 1978*, in press. In three cats paralyzed with Flaxidil, the mean increase in central conduction time between the initial negative brainstem potential (mean latency, 1.55 msec) to the prominent positive potential (mean latency 3.81 msec) was 0.13 msec for a blood alcohol level of about 200 mg/100 ml.
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Sympathetic Nervous Control of Cerebrospinal Fluid Production from the Choroid Plexus

Abstract. *The rabbit choroid plexus, responsible for the bulk production of cerebrospinal fluid, is well supplied by sympathetic nerves emanating in the superior cervical ganglia. Electrical stimulation of these nerves markedly reduces production of cerebrospinal fluid, measured by [^{14}C]inulin dilution during ventricular perfusion, whereas sympathetic denervation enhances the rate of formation.*

The mammalian choroid plexus is a highly vascularized villous structure, covered with a single layer of cuboidal epithelial cells. It is present in all four ventricles of the brain and constitutes the major site for the bulk production of cerebrospinal fluid (CSF). The fluid is formed by an active secretory process at a rate that varies considerably from species to species, but that is rather constant when expressed as a fraction of total CSF volume or on the basis of plexus weight—approximately 0.5 percent of total CSF volume is replaced by newly formed fluid every minute (*1*). Little is known about the various physiological factors controlling the rate of CSF formation from the choroid plexus; the possibility of a nervous influence has been suggested on the basis of histological studies, dating back as far as those of Benedikt in 1874, which showed the presence of nerves in the plexuses (*2*). In spite of this, the possibility that the production rate of CSF is influenced by autonomic nerves has not been seriously investigated, probably because of the lack of unequivocal ultrastructural evidence for an innervation of the plexus epithelial cells, apart from the presence of vasomotor nerves (*3*). The present study is part of a series of investigations on the innervation of the mammalian choroid plexus and the effect of autonomic nerves on bulk CSF production as measured quantitatively by the ventriculocisternal perfusion technique according to Pappenheimer and co-workers (*4*).

We used albino and randomly pigmented rabbits (weight, 2 to 3 kg) of either sex that were maintained on stan-

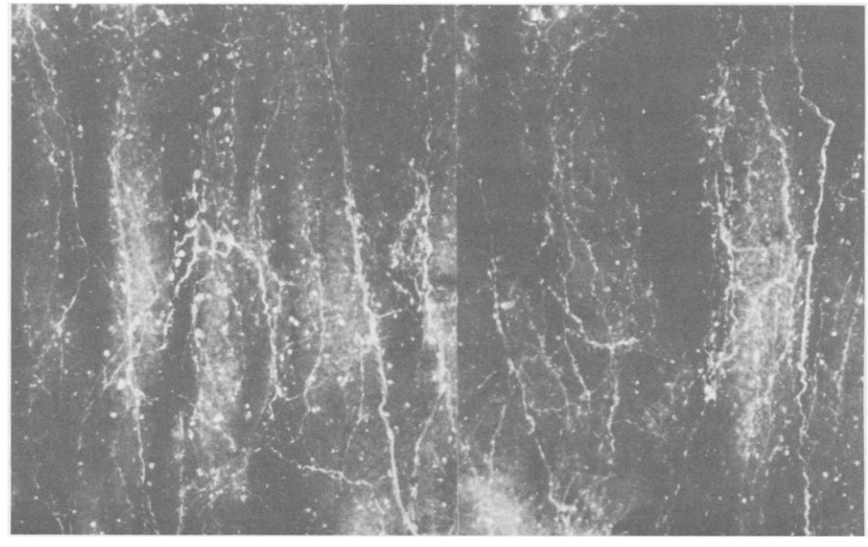

Fig. 1. Fluorescence photomicrograph of whole mount of the choroid plexus from the third ventricle of a rabbit; formaldehyde reaction. Numerous delicate adrenergic axon terminals form a network in the parenchyma among the epithelial cells. Autofluorescent cells and granules are also seen (× 65).

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