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Auditory Brain Stem Potentials in Chronic Alcohol Intoxication and Alcohol Withdrawal

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• **Auditory brain stem evoked responses were studied in unrestrained rats during periods of acute and chronic alcohol intoxication, alcohol withdrawal, and recovery. Acute alcohol administration altered the auditory brain stem potentials by a prolongation of both peak latency and central conduction time, beginning with early peaks. Similar but lesser effects affecting only the latter peaks were observed during chronic alcohol intoxication. By contrast, alcohol withdrawal resulted in a decrease in the peak latencies of auditory brain stem potentials and a facilitation of central conduction time. Recovery of the auditory brain stem potentials to the normal form required at least three to four weeks. The present study provides the first quantitative data, to our knowledge, on manifestations of alcohol tolerance and withdrawal.**

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Sensory evoked cortical potentials have been used on a number of occasions to study the effects of alcohol on the central nervous system. In animal studies, auditory cortical potentials have been shown to be reduced in amplitude by alcohol administration in moderate to high dosages.[1-4] Similar amplitude decreases for cortical potentials have been reported for visual and somatosensory stimulation.[1,3-7]

With human subjects, Gross et al[8] found a significant reduction in the amplitude of auditory cortical potentials for blood alcohol levels ranging from 40 to 150 mg/dl, with no change in peak latencies. Soveri and Fruhstorfer,[9] however, reported increased latencies for auditory cortical potentials as well as decreased amplitudes. Cortical potentials recorded over the association cortex in response to visual stimulation were also reduced in amplitude[10]; however, potentials recorded over the primary visual cortex were unchanged by low to moderate doses of alcohol.[10,11] Somatosensory potentials elicited by electrical stimulation of peripheral nerves were also reduced in amplitude,[1,5,11] although the potentials thought to originate in the primary sensory area were unchanged.[1,10,11]

At subcortical levels, there is a consensus that alcohol depresses evoked potentials recorded from the reticular formation for all sensory modalities.[1,4,6] Within the primary sensory pathways the results are less consistent. Reduction in evoked electrical activity to auditory stimuli in the inferior colliculus have been reported[6]; however, visually evoked potentials in the lateral geniculate and potentials recorded from the somatosensory thalamic nuclei were not changed.[1,5,6]

While it is clear that alcohol significantly alters brain functions, particularly at the cortical level and in the reticular formation,[1,3] the specific sensory pathways appear to be only mildly or variably affected. Further interpretation of these results is difficult, due primarily to the fact that simultaneous recordings from all of the brain structures involved in the ascending transmission of sensory-elicited events were not done. Thus, specific sites of alcohol action cannot be determined. Recently, however, techniques have been developed for recording ascending activity that can be used to alleviate this problem for the auditory system.

Auditory brain stem potentials, which are presumed to be the "far-field" reflection of electrical events generated in the brain stem auditory pathway, can be recorded with com-

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puter averaging techniques from scalp electrodes.[12] They consist of a series of seven positive waves of submicrovolt amplitude within the first 10 m/s following a click stimulation. The first peak in the waveform probably represents the compound action potentials of the auditory nerve, and the other peaks have been attributed to the subsequent ascending and probably overlapping activity in cochlear nucleus, superior olive, lateral lemniscus, and inferior colliculus.[13-16] Thus, the sequential activation in the auditory pathway can be analyzed by recording auditory brain stem potentials. This recording technique has proved to be extremely useful in detecting brain stem dysfunctions or lesions in neurological diseases[17-19] and in supplementing the other methods for determining brain death.[17,20]

We have undertaken to study the effect of chronic alcohol intoxication and alcohol withdrawal on the auditory brain stem evoked responses for several reasons: (1) previous study suggests that alcohol may affect the auditory sensory transmission at the brain stem level, as indicated by a reduction of evoked potentials in the inferior colliculus[6]; (2) symptoms and signs of brain stem dysfunction are prominent in acute and chronic alcohol intoxication; (3) we have found in rats that acute alcohol intoxication produces a significant and progressive prolongation of auditory brain stem potential peak latencies, suggesting the depressive effect of alcohol on the sensory transmission within the primary auditory pathway; and finally (4) while studying alcohol withdrawal seizures, we have found that the rats became extremely sensitive to acoustic stimuli, and the majority of alcohol withdrawal seizures are audiogenic. Thus, there is reason to believe that the auditory system is particularly sensitive to the action of alcohol in acute and chronic alcohol intoxication as well as during an alcohol withdrawal period.

METHODS

Sixteen adult Sprague-Dawley rats, weighing 200 to 250 g each, were used. With the animals under ketamine anesthesia (125 mg/kg administered intraperitoneally), two screw electrodes were placed symmetrically over the dura through the skull at 2 mm caudal to the coronal suture and 5 mm lateral to the midline, with a reference electrode placed at the frontal sinus. A polyethylene tubing of 1.22 mm in diameter was led through the nostril bone to the stomach, and the other end was secured to the skull with dental cement. At least one week was allowed for recovery from the surgery before the study of auditory brain stem evoked potentials was conducted.

Auditory brain stem potentials were obtained from the rats while they were unrestrained inside a $25 \times 50 \times 15$-cm plastic cage. The cage and the preamplifiers were housed in a large sound-attenuating chamber with a one-way window for continuous visual observation. Preliminary experiments indicated that the rats would adopt a fixed position in the cage after several minutes of exploration. The auditory stimuli were clicks of 0.1 m/s in duration delivered at a repetition rate of 10/sec via an overhead speaker 30 cm above the center of the cage. Two stimulus intensities were used: 65 dB and 45 dB above the threshold for normal human hearing. Sound pressure testing at different points within the plastic cage showed a maximum variation of only ± 1 dB. The brain electrical activity was amplified 10,000 times with a band-pass of 35 to 10,000 Hz, and averaged evoked potentials were summed over 1,024 click presentations for a 10-ms period following the stimulation. The averaged brain stem potential waveforms were then plotted on paper with an X-Y plotter. Duplicate waveforms were collected in each condition.

Auditory brain stem responses were obtained from each animal sequentially in the following order: (1) normal control recording, (2) acute alcohol intoxication, (3) alcohol intoxication during chronic alcohol intake, (4) alcohol withdrawal, and (5) recovery from chronic alcohol intoxication.

The rats were individually caged, with free access to food and water, in a room with a 12-hour dark-and-light cycle. One day prior to the beginning of chronic alcohol feeding, the recordings were taken in the control and acute alcohol conditions. In the latter, alcohol at a dose of 2 to 3 g/kg was given via the nasogastric tube and the recording begun 45 minutes to one hour following alcohol administration. The alcohol solution was prepared as 20% W/V in a liquid diet containing fats, proteins, carbohydrates, vitamins, and minerals (Isocal). This alcohol dosage yields a blood alcohol level of 100 to 150 mg/dl 45 minutes after administration. For chronic alcohol feeding, the initial dose was 3 g/kg/day, and was followed by a daily increase of 1 g/kg until a maintenance dose of 7 to 8 g/kg/day was reached. The alcohol was given in a single dose when the dosage was 3 g/kg/day. Twice daily, half doses were given—4 to 5 g/kg/day of alcohol. At the maintenance dose, the rats were given three one-third doses of alcohol per day. The schedule for alcohol feeding was as follows: 8 AM for one dose; 8 AM and 5 PM for two doses; and 8 AM, 12 AM, and 5 PM for three doses. A gradual increase in alcohol dosage is necessary for the development of alcohol tolerance and the withdrawal syndrome. Chronic alcohol feeding was continued for two weeks, and then alcohol was abruptly withdrawn. The rats would usually develop convulsions within the period of 12 to 24 hours following the last doses of alcohol, and during this withdrawal period the rats exhibit maximal sensitivity to auditory stimuli. Brain stem evoked potentials were recorded two to four days prior to the termination of chronic alcohol feeding, and again during the withdrawal period of maximal auditory sensitivity. In the chronic condition, brain stem potentials were recorded 45 minutes to one hour following administration of an alcohol dose of 2 to 3 g/kg as in the acute condition. The auditory brain stem potentials were also studied for two to eight weeks after chronic alcohol feeding was terminated in order to study the course of recovery.

The auditory brain stem potential waveforms were analyzed in terms of alterations in peak amplitude, peak latency, and central conduction time. Paired t tests were used to compare normal with various phases of alcohol feeding. Since no differences were noted between the potentials recorded from the left and right electrodes, mean values for the two electrodes were used in the analyses.

RESULTS

Clinical Observation

During chronic alcohol intoxication, the rats exhibited lethargy or stupor, impairment of righting reflex, moderate ataxia, and a decreased response to noxious stimuli. With termination of alcohol feeding, the rats first went through a depressive phase similar to that of acute or chronic alcohol intoxication, followed by a withdrawal phase during which the rats progressively became more sensitive to auditory stimulation, exhibited mild ataxia, intermittent arching posture, stereotype mouthing movements, and,

sometimes, "wet-dog shaking." The rats also showed restlessness and heightened locomotor activity, piloerection, and mild hyperventilation, and sometimes tended to assume a crouched posture. The depressive phase usually lasted eight hours following the last alcohol dose, and the withdrawal phase for the following ten to 36 hours. The majority of the withdrawal seizures seen during this time were audiogenic and were most easily elicited by jingling the keys over the cage cover, as first described by Flack et al.[21] On the jingling of the keys, the rats would immediately appear to be apprehensive or startled, which was followed by circling movements, and then tonic-clonic convulsion, usually lasting 10 to 30 seconds. Postictally, the rats usually assumed a crouched posture with "spaced-out" appearance for a few minutes. Emerging from the postictal state, the rats would exhibit intermittent myoclonus-like jerking of forelimbs or stereotype mouthing movements.

Auditory Brain Stem Potentials

The auditory brain stem potentials were remarkably consistent over the extended period of testing. Figure 1 shows the data from one animal in all five conditions. The waveforms consisted of seven positive peaks (labeled by Roman numerals) that except for peak VI, were clearly identifiable for all animals. Peak VI was quite variable (Fig 1); consequently, no data regarding it will be presented.

In addition to the auditory brain stem potentials, a cochlear microphonic potential could be identified in the waveforms for a majority of the rats. The presence of the cochlear microphonic proved to be very useful in the analysis of the latencies of the brain stem potential peaks. Since the rats were unrestrained, the position and orientation of the head was not fixed relative to the speaker; consequently, slight variations in the latency of the auditory brain stem potentials were possible due to variation in air conduction time of the acoustic stimulus. The exact time of arrival of the acoustic stimulus could, however, be determined from the latency of the cochlear microphonic, since the coch-

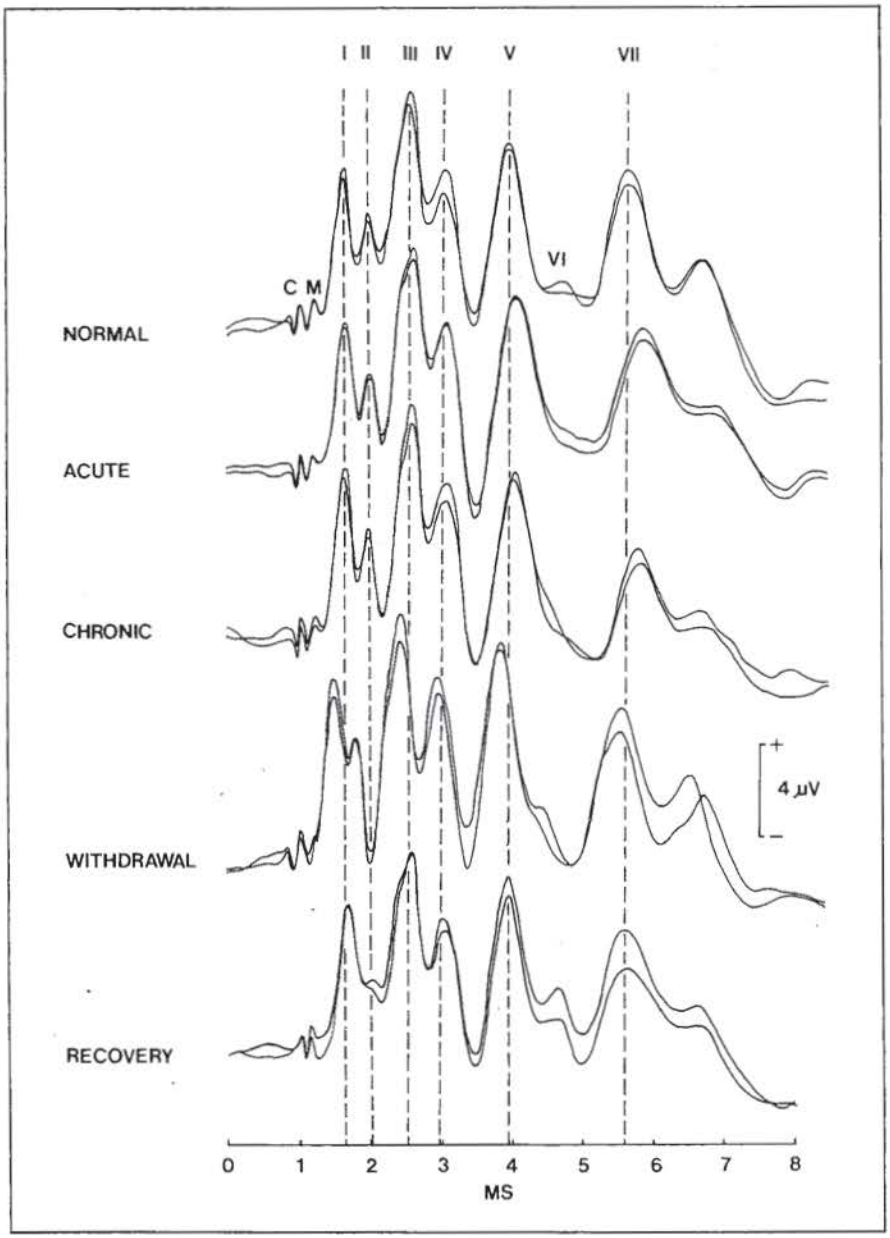

Fig 1.—Auditory brain stem potentials of a representative rat during normal control period, acute alcohol intoxication, alcohol intoxication during chronic alcohol feeding, alcohol withdrawal, and recovery from chronic alcohol intoxication (seven weeks after withdrawal). Seven positive peaks are identifiable, as designated by Roman numerals. CM represents cochlear microphonic potential.

Table 1.—Latencies of Auditory Brain Stem Potential Peaks in Rats During Control Period, Chronic Alcohol Intoxication, and Alcohol Withdrawal*

	I†	II	III	IV	V	VII
Normal	1.72 ± .08	2.01 ± .08	2.65 ± .05	3.13 ± .06	4.06 ± .08	5.89 ± .16
Chronic	1.73 ± .09	2.03 ± .07	2.69 ± .09	3.17 ± .11	4.18 ± .14‡	6.04 ± .19‡
Withdrawal	1.61 ± .10§	1.86 ± .09§	2.49 ± .08§	2.98 ± .06§	3.83 ± .08§	5.65 ± .13§

*Values represent means and standard deviations of ten rats in milliseconds after stimulus.
†Roman numerals represent the positive peaks of auditory brain stem potential as designated in Fig 1.
‡$P < .05$.
§$P < .01$.

Table 2.—Central Conduction Times From Peak I to Subsequent Peaks of the Auditory Brain Stem Potential in Rats During Control Period, Chronic Alcohol Intoxication, and Alcohol Withdrawal*

	I-II†	I-III	I-IV	I-V	I-VII
65 dB					
Normal	0.30 ± .05	0.91 ± .06	1.40 ± .05	2.32 ± .06	4.17 ± .12
Chronic	0.31 ± .05	0.95 ± .05	1.43 ± .06	2.44 ± .09‡	4.32 ± .17‡
Withdrawal	0.27 ± .04§	0.87 ± .05§	1.36 ± .06‡	2.23 ± .06‡	4.03 ± .12‡
45 dB					
Normal	. . .‖	0.89 ± .06	1.39 ± .06	2.30 ± .09	4.17 ± .19
Chronic	. . .	0.88 ± .07	1.42 ± .07	2.40 ± .09§	4.36 ± .24§
Withdrawal	. . .	0.84 ± 0.7§	1.35 ± .07§	2.22 ± .10§	4.06 ± .20

*Values represent means and standard deviations of 13 rats in milliseconds.

†Roman numerals represent positive peaks of auditory brain stem potential as designated in Fig 1.

‡$P < .01$.

§$P < .05$.

‖Peak II was often not clearly identified at 45 dB stimulation.

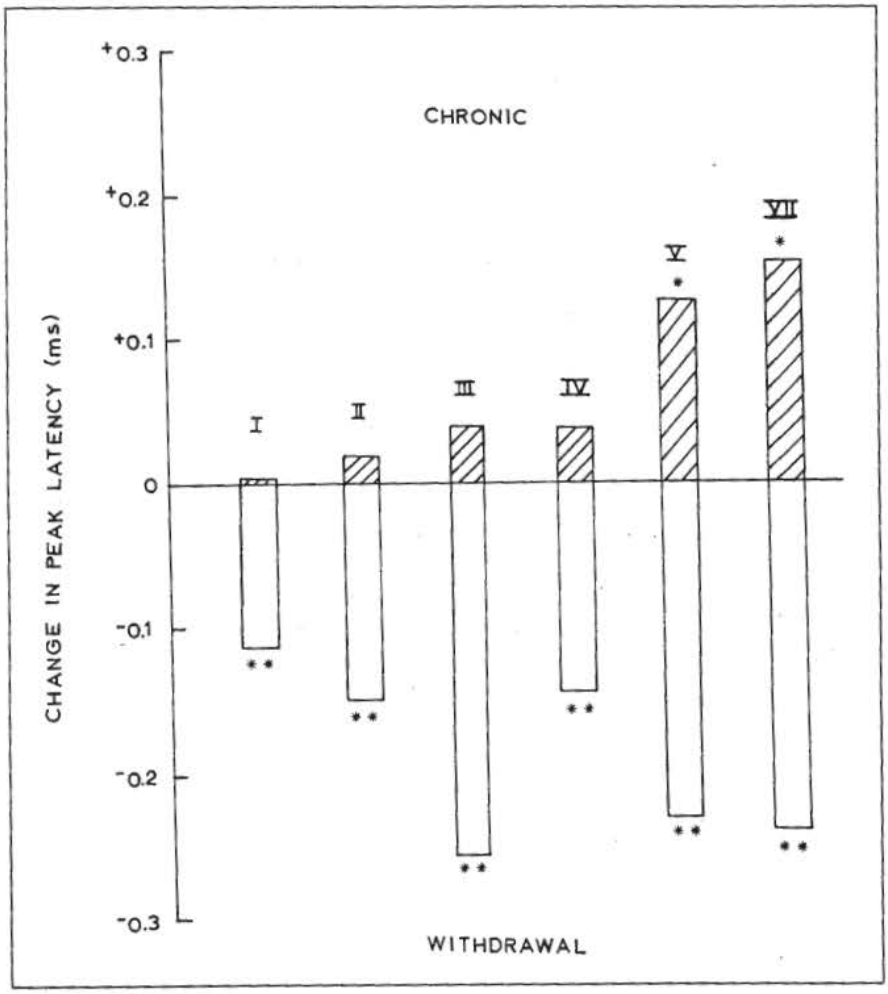

Fig 2.—Changes in mean peak latency of auditory brain stem potentials of ten rats during chronic alcohol intoxication and alcohol withdrawal period. Changes are expressed as difference in peak latency in milliseconds between normal and experimental conditions, with positive numbers indicating increase in peak latency and negative numbers indicating decrease. Click intensity was 65 dB above normal human hearing threshold. One asterisk represents $P < .05$, and two asterisks $P < .01$. Note that during chronic alcohol intoxication, prolongation of peak latency was significant for peaks V and VII, whereas during alcohol withdrawal, shortening of peak latency was significant for all peaks.

lear microphonic coincides with the deflection of the basilar membrane. Thus, in Fig 1 the waveforms have been aligned according to the cochlear microphonic latency in the normal control condition in order to eliminate latency variation in air conduction time. Whenever absolute latencies are reported, the values are for the ten rats with clear cochlear microphonic potentials and the latencies have been adjusted so that the cochlear microphonic potentials in all conditions coincided.

In addition to absolute latency measurements, the relative latencies of each peak were analyzed with respect to the latency of peak I. These measures of "central conduction time" within the auditory system are very useful because they are essentially invariant over a wide range of stimulus intensities, whereas the absolute latencies are quite sensitive to stimulus intensity. Thus, changes in central conduction time across conditions can reliably be attributed to changes in brain stem functions, in this case brought about by alcohol, independent of possible acoustic input changes. Since the central conduction time measurements do not require certain knowledge as to the time of stimulus arrival, the data for all rats, including those without clear cochlear microphonic potentials, were used.

When alcohol was first administered to the rats, the primary alteration in the auditory brain stem potentials was a prolongation of the peak latencies relative to normal. The magnitude of this prolongation progressively increased for each succeeding peak, as shown in Fig 1 (acute). For the five rats tested in the acute condition, there was a significant increase in the absolute latencies and central conduction times for peaks II through VII relative to the control condition ($P < .05$). These results indicate that alcohol has a depressive effect on brain stem auditory transmission.

Thirteen rats were tested following two weeks of chronic alcohol administration. During this stage, the dosage of alcohol (2 to 3 g/kg), which in the acute condition produced an increase in the latencies and central conduction times for peaks II through VII,

produced significant increases only for peaks V and VII (Tables 1 and 2). The progressive nature of the latency and central conduction time increases are illustrated in Fig 2 and 3. As can be seen for the central conduction times shown in Fig 3, the effect of alcohol was similar for the two stimulus intensities tested. Absolute latencies could not be determined at the lower intensity (45 dB) because the cochlear microphonic was too small to be reliably measured. Thus, it appears that following prolonged alcohol intake the effect of alcohol, while qualitatively similar to that found under acute intoxication, is less pronounced.

The effect of alcohol withdrawal on the auditory brain stem potentials was a striking reversal over that found under alcohol intoxication (Fig 1). As shown in Fig 2 and Table 1, all peak latencies were significantly shorter than those found in the normal condition. Likewise, the shortening of central conduction time was significant for all peaks (Fig 3 and Table 2).

Five rats were followed up during the recovery period following alcohol withdrawal. As late as three to four weeks after the last alcohol dosage, four of the five rats still showed slightly shortened peak latencies relative to normal. This effect was absent by eight weeks. Thus, recovery from chronic alcohol administration, as reflected in the auditory brain stem potentials, appears to be a lengthy process.

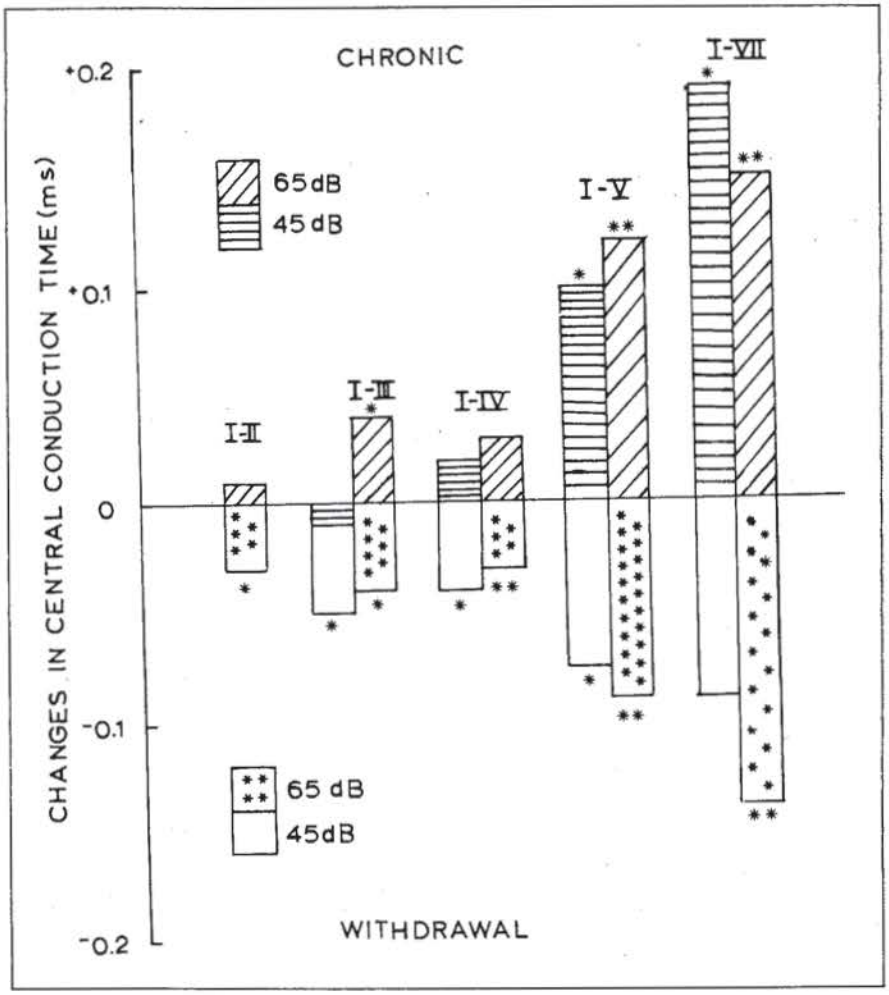

Fig 3.—Changes in mean central conduction time of auditory brain stem potentials of 13 rats during chronic alcohol intoxication and alcohol withdrawal period. Central conduction time is measured in milliseconds from peak I to subsequent individual peaks. Changes are expressed as difference in central conduction time in milliseconds between normal and experimental conditions, with positive numbers indicating increase in central conduction time and negative numbers indicating decrease. Effects of two stimulus intensities, 45 and 65 dB above normal human hearing threshold, are presented. One asterisk represents $P < .05$, and two asterisks $P < .01$. Prolongation of central conduction time of peaks I through VII for 45 dB stimulation in alcohol withdrawal is not significant because of large degree of variation.

COMMENT

Several conclusions can be drawn from the results of this study. First, alcohol has widespread effects on the central auditory pathways. In the acute condition, alcohol significantly increases the latency of the brain stem potential peaks starting with peak II and yields progressively increasing central conduction times for successively later peaks. This suggests that acute alcohol ingestion depresses auditory sensory transmission within the CNS.

Second, a tolerance to the effect of alcohol on transmission occurred during chronic intake. An equivalent alcohol dose yielded less pronounced effects on the auditory brain stem potentials during chronic alcohol intoxication than during an acute alcohol intoxication. Only the latest peaks (V and VII) were significantly delayed in the chronic condition, whereas in the acute condition peaks II through IV were delayed.

Third, during alcohol withdrawal there was a facilitation of transmission in the central auditory system. The facilitation may have taken two forms: a peripheral change in stimulus effectiveness that yielded an overall decrease in peak latencies beginning with peak I, and a central change that yielded decreased central conduction times. The second mechanism appears to be essentially the reverse of that found during alcohol intoxication. The mechanism for the intensity-like change remains obscure; however, several possibilities exist, including changes in middle ear muscle activity, receptor sensitivity, or efferent effects on the inner ear.

The most striking aspect of these alcohol-related changes in auditory brain stem activity is that they mirrored the clinical observations. During acute alcohol administration,

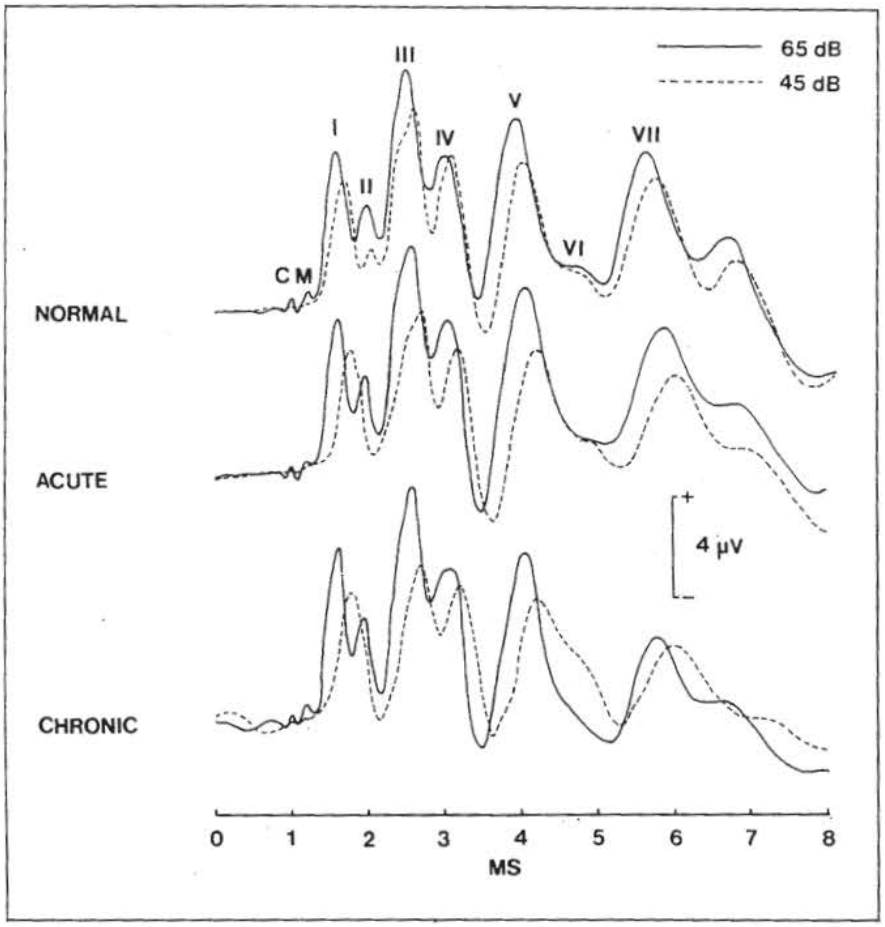

Fig 4.—Effect of stimulus intensity on auditory brain stem potentials of a representative rat, during normal control, acute, and chronic alcohol intoxication. Solid line represents auditory brain stem potentials obtained with click intensity of 65 dB above normal human hearing threshold; broken line, 45-dB click stimulation. Note that during acute and chronic alcohol intoxication, there was no appreciable changes in amplitude of auditory brain stem potentials as compared to that in normal control recording. However, there was decrease in amplitude when stimulus intensity was reduced in both acute and chronic alcohol intoxication.

the rats uniformly exhibited signs of significant intoxication, whereas in the chronic condition they appeared to be less affected. Similarly, the depressive effect on the brain stem auditory transmission was less marked. During withdrawal, on the other hand, the rats were hyperexcitable and audiogenic seizures were often elicited by jingling of keys, and the auditory brain stem potentials seemed to reflect this increased excitability or increased auditory sensitivity.

Finally, the recovery time for the auditory brain stem potentials to reach normal, prealcohol latencies was remarkably long. Appreciable latency decreases were found for most rats tested during recovery for three to four weeks after the last alcohol dose, although the latency decreases were significantly less than during the immediate withdrawal phase. The alcohol effects, however, were absent by eight weeks after withdrawal.

It is highly unlikely that the changes in central conduction time under acute and chronic alcohol intoxication were due to changes in stimulus intensity because of variations in head position. In all three conditions (normal, acute, and chronic), central conduction time was not altered by reducing the signal intensity by 20 dB (Table 2). Furthermore, there were no significant changes in the peak-to-peak amplitudes of the auditory brain stem potentials in the acute and chronic conditions as compared to normal, whereas the amplitude was reduced when lowered stimulus intensity was given (Fig 4).

Previous studies have shown that alcohol predominantly affects the reticular activating system and cerebral cortex while the primary sensory pathways are relatively spared.[1,2] However, our previous and present studies strongly suggest that alcohol ingestion and withdrawal affect the primary auditory pathways; these effects can be appreciated even in the most peripheral part of the auditory system, as indicated by the change in latency in peak I in withdrawal and the change in conduction time between peak I to II in both alcohol intoxication and withdrawal. Whether this peripheral effect of alcohol is due to changes in middle ear muscle activity, receptor sensitivity, or auditory nerve transmission is not clear from this study and further investigation is needed. Also, the sites of central action of alcohol are not clear. However, since there is a progressive prolongation of subsequent peak latencies of the auditory brain stem responses with concomitant progressive increase in central conduction time, alcohol appears to exert a more pronounced depressive effect when more synapses or central connections are involved in auditory transmission.

Since sites of sequential activation of auditory transmission in the brain stem can be analyzed by brain stem auditory evoked response, this method has been used for the detection of brain stem lesions in neurological diseases.[17-19] It is conceivable that the auditory brain stem response can be used to differentiate uncomplicated alcohol intoxication from other neurological complications associated with alcoholism where structural lesions are present, such as in the Wernicke-Korsakoff syndrome and central pontine myelinolysis. Presumably, in the former condition, only changes in peak latency and central conduction time of the auditory brain stem response will be observed, but the waveforms will remain relatively unchanged, whereas in the latter condition, distortion and even absence of components of the auditory brain stem response will be present, as previously reported.[17-19,22]

The shortening of peak latencies and central conduction time of the auditory brain stem response during alcohol withdrawal is striking. This is the first quantitative data indicating the electrophysiological concomitant of increased sensitivity to sensory stimulation during alcohol withdrawal. The progressive shortening of peak latency and central conduction time of the auditory brain stem response also suggests increased facilitation on the auditory transmission where more synapses or connections between brain stem relay nuclei are involved. During alcohol withdrawal, an increased cortical excitability is shown by a decreased threshold for seizures by pentylenetetrazol in animals[23] and an increase in photosensitivity in humans.[24] Since this study also indicates an increased sensitivity to auditory stimulation within brain stem auditory pathways, it is conceivable that the hyperexcitable state of the brain during alcohol withdrawal is widespread. Furthermore, this study also suggests that the CNS hyperexcitability during alcohol withdrawal can be quantitatively demonstrated.

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