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AUDITORY BRAIN STEM POTENTIALS WITH ALCOHOL [1]

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Ethyl alcohol is known to be associated with a decrease in the amplitudes of sensory evoked potentials, particularly those originating from association areas of the cortex (Schweigerdt et al. 1965; Gross et al. 1966; Himwich et al. 1966; DiPerri et al. 1968; Lewis et al. 1969, 1970; Soveri and Fruhstorfer 1969; Begleiter et al. 1972; Himwich and Callison 1972; Salamy and Williams 1973; Kalant 1974; Perrin et al. 1974; Grenell 1975; Rhodes et al. 1975; Obitz et al. 1977; Kopell et al. 1978). At more peripheral levels of the sensory systems the effect of alcohol is generally markedly reduced or absent (Dravid et al. 1963; Schweigerdt et al. 1965; Himwich et al. 1966; DiPerri et al. 1968; Lewis et al. 1969, 1970; Himwich and Callison 1972; Nakai et al. 1973; Salamy and Williams 1973; Rhodes et al. 1975), though amplitude reductions for auditory evoked potentials have been observed as far peripherally as the inferior colliculus (DiPerri et al. 1968). At present, however, it is impossible to conclude at what level of sensory transmission alcohol has its first effect, because simultaneous recordings of evoked potentials from throughout the brain have not been performed.

The auditory system is uniquely suited for such a study because the sequential activation of neural structures along the brain stem auditory pathway can be recorded from electrodes as far distant from the brain stem as the scalp (Jewett et al. 1970; Plantz et al. 1974). The 'far-field' potentials of the auditory pathway consist of a series of 7 positive waves within the first 7—10 msec after acoustic stimulation. The first of these waves has been attributed to activity in the auditory nerve, and the subsequent waves may represent sequential activity in cochlear nucleus, lateral lemniscus and inferior colliculus (Jewett 1970; Jewett et al. 1970; Picton et al. 1971, 1974; Lev and Sohmer 1972; Sohmer et al. 1974; Buchwald and Huang 1975; Starr and Achor 1975; Salamy and McKean 1976; Starr and Hamilton 1976; Stockard et al. 1976; Stockard and Rossitor 1977). Thus, it may be possible to determine the level at which alcohol influences this sensory system by measuring its effect on the various auditory brain stem potential peaks.

A second unresolved issue is the extent to which evoked potential latencies, as well as amplitudes, are affected by alcohol. There are conflicting reports as to whether auditory and visual potentials are delayed by alcohol (Gross et al. 1966; Soveri and Fruhstorfer 1969; Obitz et al. 1977), though no changes in evoked potential latency under alcohol for somatosensory stimulation have been reported. Most studies, however, have focused on cortical evoked potentials, for which small latency changes may not be resolvable due to the relatively long durations of these potentials. A more sensitive procedure for evaluating latency effects of alcohol might be to record brain stem potentials, which are much more discrete in both time and place of origin.

In the present report, the effect of alcohol

on auditory far-field brain stem potentials was studied in the unrestrained rat (Experiment 1) and in the awake cat paralyzed with Flaxedil ® (Experiment 2).

Experiment 1

Methods

The subjects were 6 adult rats, weighing 200—250 g. Under ketamine anesthesia (150 mg/kg, i.p.), dural electrodes were implanted at symmetric points 6 mm lateral to the midline and 1 mm posterior to the coronal suture, with a reference electrode in the frontal sinus. A nasogastric polyethylene tube was implanted for alcohol administration. At least 1 week was allowed for recovery following surgery before evoked potential recordings were made.

The brain electrical activity was amplified 10k times with a bandpass of 35—10,000 Hz. Brain stem potentials to 1024 click stimuli were averaged on-line with a resolution of 40 μsec/point. The click stimuli (0.1 msec duration) were delivered at a rate of 10/sec via a speaker located 30 cm above the floor of a roofless 15 cm $\times$ 30 cm cage containing the animal. The cage was located in a sound attenuating chamber and had a sawdust covered floor, resulting in a maximum peak sound field variation of ±1 dB. Two stimulus intensities were tested; 65 dB and 45 dB above threshold for normal human hearing at a distance of 30 cm from the speaker. The animals were unrestrained, except for the confines of the cage and lightweight wires connecting the electrodes to the amplifiers. Following a few minutes of exploration, they would settle into a crouched, resting position. The animals were under continuous visual observation and recordings were taken only when the animals were stationary and properly situated relative to the speaker.

Following a series of replicated recordings of brain stem potentials in a normal, pre-alcohol condition, an alcohol solution (20% w/v in Isocal ®) was administered via the naso-

gastric tube. The dose, 2.5 g/kg, was selected because it yielded a blood alcohol level of about 100—150 mg% (mg/100 ml) 30 min to 1 h after ingestion. The dosages and corresponding blood alcohol levels were determined prior to this study on a separate group of animals. Brain stem potentials were again recorded 30 min to 1 h after the alcohol was administered. At that time the animals appeared intoxicated and exhibited drowsiness and mild to moderate ataxia.

Results

Auditory brain stem potentials (65 dB clicks) for two representative animals are shown in Fig. 1. Replicated wave forms are presented in order to demonstrate the reproducibility of the data. As can be seen, the wave form, consisting of 7 positive peaks, was extremely consistent across animals and conditions. The only exception was peak P6 which was not always discernible, consequently no conclusions will be reached concerning that peak.

The latencies of each prominent peak in the normal, pre-alcohol condition are indicated by dashed lines in Fig. 1. A comparison of the wave form peaks in the alcohol condition with the dashed lines illustrates that the primary effect of alcohol on the brain stem potentials was a progressive shift to longer peak latencies, increasing in magnitude with each successive peak. This effect was found for all 6 animals.

In order to quantify the latency changes with alcohol, the latency of each peak was measured with respect to the latency of P1. This measure, termed the 'central conduction time', has the advantage that it compensates for variations in the air-conduction time of the stimulus due to changes in the distance of the speaker from the animals' ears. It has the further advantage that central conduction time has been shown to be invariant over a wide range of stimulus intensities, including those used here (Hecox and Galambos 1974; Picton et al. 1977; Starr 1977). Thus the possibility of confounding,
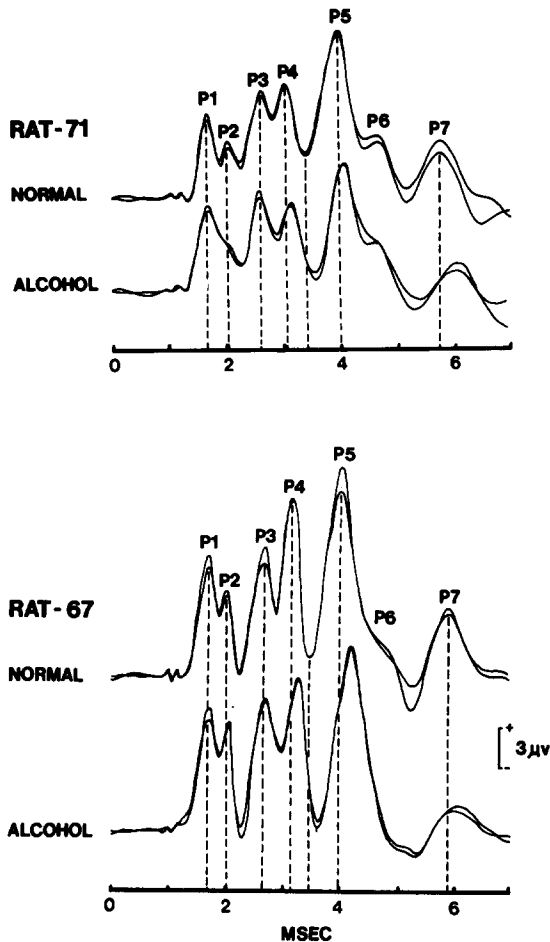
Fig. 1. Auditory brain stem potential wave forms for two rats, before and after alcohol. Stimulus intensity, 65 dB. Replicated wave forms are shown in each case.

times across all 6 animals for the two stimulus intensities before and after alcohol. Also shown are the changes in central conduction time due to the alcohol and the significance levels of each change. The significance levels were determined by t-tests (two-tailed) for matched pairs (before and after alcohol). At both stimulus intensities central conduction time increases were evident, even for relatively early peaks (beginning with P3) and became progressively larger for each succeeding peak.

In order to insure that the assumption regarding the intensity independence of central conduction time was valid, the central conduction times for each peak at the two stimulus intensities were also compared. No significant effects were found in either alcohol condition (see Table I). Thus it is unlikely that an unforeseen variation in stimulus intensity could account for the changes in central conduction time under alcohol.

Recently there have been reports that changes in body temperature can affect the latencies of brain stem potentials (Jones et al. 1977). In order to insure that the alcohol effect was not secondary to a change in body temperature, additional control experiments were conducted. Two rats were tested as described above, except that during the recording periods they were restrained with cloth wrappings so that body temperature could be monitored with a rectal thermometer. Under these conditions where pre- and post-alcohol temperatures were identical, the effect of alcohol was the same as described above. Four other rats were administered alcohol, returned to their home cages and after 45 min their temperatures were recorded. Alcohol dosages of the level used here (2.5 g/kg) yielded temperature changes of less than ±1°C. Thus it is unlikely that body temperature was a source of the alcohol effect described here. (Additional data relevant to this issue will be presented in Experiment 2.)

Two analyses of the amplitudes of the brain stem potential peaks were also con-

intensity-dependent variations in the brain stem potentials due to changes in head or pinna orientation were also avoided. The effects of alcohol could then be attributed to changes in neural conduction within the brain stem.

Since no differences between the evoked potentials recorded from the two symmetrical electrode sites were noted, mean values across the two sites and two replications were calculated for each condition for each animal. Table I lists the mean central conduction

TABLE I

Central conduction times (latency with respect to P1) in msec for each peak in the two conditions (normal and alcohol) at each stimulus intensity (65 dB and 45 dB). The significance levels for the changes in central conduction time under alcohol are also shown.

Stimulus	Condition	Peak					
		P2	P3	P4	P5	P6	P7
65 dB	Normal	0.31	0.92	1.38	2.32	—	4.07
	Alcohol	0.34	0.98	1.44	2.44	—	4.35
	Δ	0.03	0.06	0.06	0.12	—	0.28
	P	—	<0.01	<0.05	<0.01	—	<0.05
45 dB	Normal	—	0.87	1.35	2.26	—	4.04
	Alcohol	—	0.96	1.44	2.43	—	4.43
	Δ	—	0.09	0.09	0.17	—	0.39
	P	—	<0.01	<0.05	<0.05	—	<0.05

ducted; with respect to a baseline voltage over the first 1 msec of the wave form (which was prior to the arrival of the air-conducted stimulus at the animal's ears), and with respect to the preceding or following negative peak. For the peak-to-peak amplitude measure there were no significant changes due to alcohol at either stimulus intensity. Measured with respect to baseline, however, there was an overall negative shift of the wave form (approximately 1 μV) under alcohol beginning with peak P3 and continuing through the remainder of the epoch. Analyses of the amplitudes as a function of stimulus intensity yielded significant amplitude changes for all peaks, measured both peak-to-peak and base-to-peak. Thus, both in terms of the changes in brain stem potential amplitudes and central conduction times, the effect of alcohol could be differentiated from one due to stimulus intensity.

Experiment 2

The results of the first experiment strongly suggested that alcohol has a depressive effect on conduction within the brain stem auditory system. In that experiment the measures of neural conduction were selected specifically to avoid the confounding effects of variations in stimulus intensity or stimulus arrival time. In order to insure that there was complete control of the acoustic input and such intervening mechanisms as the middle-ear muscles, a second experiment was conducted with 3 adult cats immobilized with Flaxedil ®.

Methods

The animals were maintained on artificial respiration, the body temperature was monitored with a rectal thermometer and the animals were maintained at a constant temperature. Monaural, 0.1 msec clicks were presented at 65 dB sensation level (for a normal hearing human) at a rate of 25/sec via a flexible plastic tube inserted into the external auditory meatus. The animal was situated within a double-walled acoustic chamber. Needle electrodes were inserted under the skin at the vertex referred to a second needle at the back of the neck. A third needle at the forelimb served as a ground. The brain electrical activity was amplified 10k times with a bandpass of 100—3 kHz. Averaged evoked potentials were summed over 100—400 click presentations.

Following recording of brain stem potentials in a normal, pre-alcohol condition for 1 h, alcohol (20% w/v) was administered via

a gastric tube. Each animal received a total dosage of 2—3 g/kg body weight. Additional recordings were taken over a 2—3 h period. Blood samples were taken at regular intervals.

Results

The data are summarized in Fig. 2 where the wave forms for two animals at the indicated blood-alcohol levels are presented. The body temperatures were identical for the pre- and post-alcohol recordings (37°C). The wave forms for the third animal were comparable to those shown. As was the case for the rats, alcohol had the effect of delaying the brain stem potential peaks, and the amount of the delay increased with successively later peaks. The earliest peaks appeared to be essentially unaffected.

While specification of analogous peaks in the rat and cat brain stem potentials is

Fig. 2. Same as Fig. 1 for two cats.

difficult because of differences in the size of the brain, anatomy and electrode sites, it can be noted that the increases in central conduction time under alcohol for the two species were roughly comparable. For the cats, the mean increase in the central conduction time between the negative potential at 1.5—2.0 msec and the prominent positive potential at 3.5—4.0 msec was 0.13 msec for a blood-alcohol level of about 200 mg%.

Also, as for the rats, no systematic changes in the amplitudes of the potentials were seen under alcohol, though the number of subjects was too small to reach a statistically valid conclusion on that point.

Discussion

Most discussions of the effects of alcohol on the central nervous system have emphasized the role of alcohol in modifying the electrical activity of the cortex and/or the reticular formation. The relatively marked depression of evoked potentials recorded from those areas is consistent with the profound changes in behavior and attention normally observed during alcohol intoxication. The sensory pathways, on the other hand, have appeared to be relatively spared, even up to the level of primary sensory cortex. Only in the auditory modality was a subcortical structure in the sensory pathway (inferior colliculus) reported to be affected by alcohol (DiPerri et al. 1968). It is now clear from the results of the studies reported here, that acute administrations of alcohol in moderate amounts can influence sensory transmission in the auditory system throughout the brain stem. While the absolute magnitudes of the changes in central conduction time associated with alcohol ingestion were small, the results demonstrate a reliable alteration in brain stem function. This is perhaps not surprising since clinical signs of brain stem dysfunction such as ataxia, dysarthria, vertigo and stupor are characteristic of alcohol intoxication.
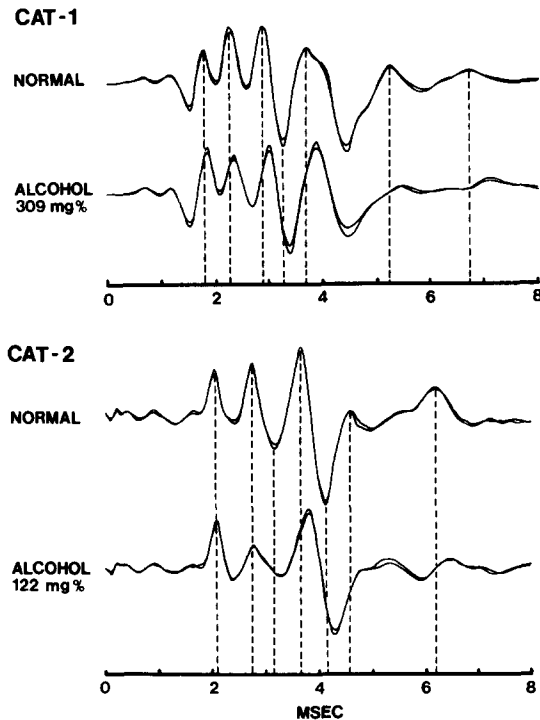
The primary effect of alcohol was to

increase the latencies of the brain stem potential peaks. Moreover, the magnitude of the latency change was progressively larger for later peaks. Since the overall wave form morphology was unchanged by alcohol and because of the progressive nature of the increase in latency for successive peaks, it appears that the effect of alcohol on neural activity is relatively uniform throughout the brain stem structures responsible for the far-field wave form.

The earliest statistically significant delay in the brain stem wave form was found for peak P3 in the rat. This peak is commonly attributed to activity from the superior olivary nucleus of the medulla (Jewett 1970; Jewett et al. 1970; Picton et al. 1971, 1974; Lev and Sohmer 1972; Sohmer et al. 1974; Buchwald and Huang 1975; Starr and Achor 1975; Salamy and McKean 1976; Starr and Hamilton 1976; Stockard et al. 1976; Stockard and Rossitor 1977). While these latency data were reported in terms of the central conduction times from P1, separate analyses of P1 latency with respect to the absolute stimulus onset and to the latency of the cochlear microphonic potential, which was identifiable in most wave forms, provided no evidence for an effect of alcohol on that peak. Since the P1 peak most likely represents the compound action potential of the auditory nerve (Picton et al. 1974), this suggests that alcohol exerts its effects on central structures, sparing the auditory end organ. It is possible, however, that the effects on the most peripheral structures were merely too small to be resolved with the techniques used here since variations in cochlear potentials have been reported elsewhere (Gieldanowski 1965).

It is important to note that the depressive influence of alcohol on sensory transmission shown here occurs even in the absence of variations in body temperature, since delayed potentials have been reported during hypothermia (Jones et al. 1977). Also, any extraneous effects of variations in the acoustic stimulus were effectively controlled in Experiment 2, where the middle-ear muscles, which are reportedly affected by alcohol (Børg and Møller 1967), were paralyzed and the auditory stimulus was coupled directly to the ear.

At present there is still debate about the sites of origin of each peak in the brain stem potential wave form. Likewise there are questions remaining about the specific neural activity underlying them, in terms of the contributions of summated action potentials and synaptic events. Consequently, no firm conclusions are possible from these data regarding the mechanisms of action of alcohol in the brain stem. One interesting aspect of the data, however, is that while the latencies of the potentials were clearly affected, concomitant changes in peak-to-peak amplitude which are normally associated with latency changes throughout the nervous system were not seen. This would suggest that the neural events were delayed without a decrease in the synchrony of the events.

Even without detailed knowledge of all the underlying mechanisms, however, the use of brain stem potentials has in many instances provided important information about the brain stem and about brain stem dysfunction in neurological disease (Lev and Sohmer 1972; Starr and Achor 1975; Starr and Hamilton 1976; Stockard et al. 1976; Stockard and Rossitor 1977). The results of this study suggest that the use of brain stem potentials can be further usefully applied to the study of central nervous system under depressant and stimulant drugs.

Summary

Auditory brain stem potentials were recorded from unrestrained rats and from cats paralyzed with Flaxedil ®, before and after ingestion of intoxicating dosages of alcohol. The acute effect of alcohol was a cumulative increase in the central conduction times of successive brain stem potential peaks. Statistically significant latency changes were

found for peaks attributed to neural structures as far peripherally as the medulla. This depressive influence of alcohol on sensory transmission was independent of variations in stimulus intensity and body temperature.

Résumé

Potentiels auditifs du tronc cérébral et alcool

Les potentiels auditifs du tronc cérébral ont été enregistrés chez des rats non maintenus et des chats paralysés au Flaxedil ® avant et après ingestion de doses toxiques d'alcool. L'effet aigu de l'alcool consiste en une augmentation cumulative des temps de conduction centraux des pics des potentiels du tronc cérébral consécutifs. Des modifications de latence statistiquement significatives s'observent pour des pics attribués à des structures nerveuses aussi périphériques que la moelle. Cette influence dépressive de l'alcool sur la transmission sensorielle est indépendante des variations de l'intensité du stimulus et de la température corporelle.

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