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Excitability Cycle of Somatosensory Evoked Potentials during Experimental Alcoholization and Withdrawal

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Abstract. It has been postulated that withdrawal from alcohol ingestion by alcoholics, is manifested by hyperexcitability of the central nervous system.

In order to study changes in brain excitability in human alcoholics during intoxication and withdrawal, we used the recovery cycle of somatosensory evoked potentials. A recovery function was always determined in the morning (10 h after the last drink), during the three days of baseline, four days of alcoholization, and the four days subsequent to withdrawal from alcohol.

Our results indicate a progressive increase of brain excitability starting with the intoxication period and reaching asymptote with the first day of total alcohol withdrawal. During the subsequent days of testing the recovery function decreases, approaching the level obtained during baseline determinations.

Key words: Alcoholics — Intoxication — Withdrawal — Brain Hyperexcitability.

The occurrence of withdrawal signs and symptoms upon cessation of alcohol ingestion by alcoholics is evidence of physiological dependence. Excellent descriptions of the alcohol withdrawal syndrome have been reported by Isbell, Fraser, Wikler, Belleville, and Eisenman (1955), Victor and Adams (1953), Mendelson (1964), and Gross, Lewis, and Hastey (in press). The various clinical reports fall on a continuum of increasing severity, from the mildest case of tremulousness, sleeplessness and irritability, increasing through hallucinatory states and seizures, to the severest type, delirium tremens. It is important to realize that all of these states are characterized by various degrees of hyperexcitability and hyperactivity of the central nervous system.

While the critical determinants of the onset of withdrawal symptoms are unclear, it is our contention that during periods of intensive drinking, physical dependence mechanisms are already in effect. The occurrence of withdrawal symptoms after a short period of exposure to alcohol has been reported by Mendelson, Stein, and McGuire (1966) who compared the effects of a four-day period of alcoholization in 4 alcoholic and 4 normal subjects. Following cessation of drinking, two of the alcoholic subjects

showed some withdrawal symptomatology while none of the control subjects did. The authors interpreted their results as indicating that alcohol addicts have a predisposition to develop withdrawal symptoms.

A recent study by Branchey, Rauscher, and Kissin (1971) demonstrated that the establishment of a state of physical dependence increased the incidence of withdrawal symptoms in a subsequent period of alcoholization. The administration of an alcohol diet did not induce any noticeable withdrawal symptomatology in animals not previously exposed to alcohol. On the other hand, when previously alcohol-dependent animals were subjected to the same procedure, 50% of them demonstrated a severe withdrawal syndrome.

Mello and Mendelson (1969) reported that partial withdrawal signs appear in subjects who have been drinking small amounts of alcohol for a short period of time. Similar findings have been reported in animals by LeBlanc, Kalant, Gibbins, and Berman (1969). These investigators trained rats to run a motor-driven belt which was suspended over an electrified grid. If the animal was unable to perform this task, he received an electric shock when he strayed from the belt to the grid. They observed an exaggerated escape response following shock subsequent to ethanol administration. LeBlanc *et al.* (1969) interpreted this exaggerated escape response as a sign of hyperirritability which occurred after the peak effect of each test dose of ethanol. It is quite possible that such hyperexcitability represented a partial withdrawal effect in the rat.

Seevers and Deneau (1963) have defined physical dependence as a state of latent hyperexcitability which develops in the central nervous system following administration of morphine, alcohol, barbiturates and other pharmacological agents. Recovery functions of somatosensory evoked potentials have been used to measure central nervous system excitability (Shagass, 1972). Pairs of somatosensory stimuli were delivered and the effect of changing the time interval between the two stimuli of a pair was examined. The size of the second response relative to the first response is indicative of the extent to which responsiveness has recovered after a particular time interval has elapsed. Shagass (1972) has reported that this excitability function is quite sensitive to numerous pharmacological agents. Bergamasco (1966) found that pentamethylenetetrazol, a central nervous system stimulant having a recruiting and synchronizing action on cortical neurons, shortens the recovery cycle of visual evoked potentials considerably. Gartside, Lippold, and Meldrum (1966) reported that lithium carbonate decreased the excitability cycle of somatosensory evoked potentials.

In order to measure hyperexcitability of the central nervous system in the present experiment, we chose to study the recovery function of somatosensory evoked potentials. It is our hypothesis that in alcoholics, as

intensive drinking progresses, there is an increase in central nervous system excitability as measured by the recovery cycle of somatosensory evoked potentials. The recovery cycle of the evoked response corresponds to the duration of the relative refractivity of the cortical neurons following their response to a corticopetal stimulus (Bergamasco, 1966).

Methods

Subjects. The experiment was performed on four male alcoholics with a mean age of 36. All subjects reported high alcohol intake for a minimum period of 10 years and were admitted to the hospital because of severe drinking problems. They volunteered to participate in the study after a total abstinence period of three weeks. None of the patients received medication during the study and during the two weeks preceding the study.

Recovery Function. The recovery function is determined by administering pairs of stimuli separated by varying intervals; the size of the second response (R_2) compared with the first (R_1), indicates the extent to which responsiveness has recovered after a given interval of time.

Somatosensory responses were evoked by stimulating the median nerve of the right wrist through electrodes placed on the skin 3 cm apart (anode distal). A ground electrode was placed proximal to the cathode. The stimulus was a pulse of 1 msec duration at intensity 3 ma above the subject's thumb twitch threshold. The source of the pulse was a constant current stimulator, triggered and timed by means of a Grass 28 stimulator and isolation unit. Recording electrodes were placed in the parasagittal plane 7 cm left of the midline. The active lead was 2 cm behind a line from vertex to external auditory meatus and the other was 6 cm anterior to it. The EEG was amplified with a Grass Model 78 and fed into a Computer of Average Transients (CAT 1000) for algebraic summation. Analysis time of 512 msec was used. In order to obtain accurate measurements of the responses, a calibration pulse was placed on each sweep in the last 20 ordinates. Nine interstimulus intervals were used for recovery cycle determinations. These were as follows: 5, 10, 15, 20, 40, 60, 80, 100, 120 msec. All interstimulus intervals were randomized across subjects. Stimulus repetition frequency was variable from 1 to 3 sec. Each stimulus sequence involved alternating presentation of two stimulus pairs and two unpaired stimuli. Fifty paired and 50 single stimuli were summated. Responses to unpaired stimuli (R_1) were stored in one channel of the computer. Responses to both paired and unpaired stimuli were stored in the other channel, but in opposite polarity, so that the resulting algebraic sum represented $R_1 + R_2 - R_1$. This automatic subtraction procedure permitted independent visualization of R_1 and R_2. The evoked potentials were written out on a Moseley XY plotter.

Recovery functions were derived only from the initial, or primary response. The amplitude recorded was the initial negative-positive component as measured by Shagass and Schwartz (1961). The conventional method of displaying recovery functions in neurophysiology has been to plot the ratio of the second to the first response (R_2/R_1). However, this approach makes two assumptions: (1) the regression of R_2 upon R_1 must be rectilinear, (2) the regression line must pass through the origin. Since most data do not meet these criteria, it was necessary to use a method other than the ratio to evaluate differences in recovery. The method developed by Shagass (1972) involves adjusting the R_2 values at each separate interstimulus interval by means of the regression equation relating R_2 to R_1 for that specific interstimulus interval. The regression equations are used to adjust the R_2 values for

their covariance with R_1. The final recovery function is made up of adjusted R_2 values which are used in the final tastistical analyses.

Experimental Design. Each subject was required to abstain from alcohol for a period of three weeks prior to the experiment. During the three weeks of the experimental procedure, recovery function determinations were always performed in the morning at 10 A.M., and were sampled every day in the following fashion:

On the first two days of testing, baseline recovery function records were obtained (Thursday and Friday). On the following Sunday, the patient received a half-dose of alcohol, 1.6 g/kg (whiskey 80 proof) which he drank in 10 equal doses between 2 P.M. and 12 P.M. Recovery functions were determined the following morning, 10 h after his last drink. On Monday, Tuesday, Wednesday and Thursday, he received a full dose of alcohol (3.2 g/kg). In each instance, we studied changes in excitability cycles the following morning, 10 h subsequent to his last drink. On Friday, alcohol was suddenly withdrawn and a recovery function determination was obtained Saturday morning. Finally, records were obtained on Monday, Wednesday and Friday mornings of the following week.

In order to examine the effect of time on the recovery function, the identical three-week procedure was repeated, once with alcohol and once without. Half of the patients were first subjected to the experimental (alcoholization) condition for three weeks, and then, after a rest period of one week, were subjected to the control

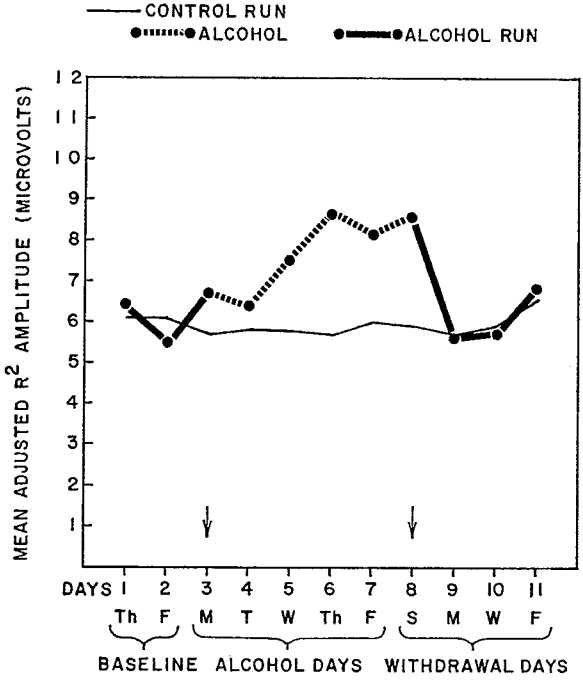

Fig. 1. Mean adjusted R_2 amplitude for all subjects under the control and experimental (alcohol) conditions. Days indicated represent recovery function determinations obtained 10 h subsequent to alcohol ingestion

condition for another three weeks. The other half of the subjects received the control condition first, and then the alcoholization condition.

Results

In order to compare the data obtained during the experimental run with that of the control run, we summarized the data in the following fashion: a mean recovery function score was derived for all nine interstimulus intervals, and these data were partitioned into three categories baseline, alcoholization and withdrawal. We then proceeded to analyse the data with a two-way analysis of variance with repeated measurements on two factors.

For the baseline, the difference between the control run and experimental run is not statistically significant.

For the alcoholization run, the main effect for treatment yielded an F ratio of 21.73, significant at $P < 0.01$. The main effect for days yielded an F score of 3.88 ($P < 0.05$).

The analysis for variance for the withdrawal data did not yield a significant F ratio for the treatment main effect. However, the main effect for days yielded an F score of 5.75 ($P < 0.05$). Only the first day of withdrawal (day 8) is different ($P < 0.05$) from the control data.

As can be seen from Fig. 1, the excitability cycle of somatosensory evoked potentials increases as drinking progresses and appears to reach a peak on the first day of withdrawal from prolonged alcohol ingestion.

Discussion

These data certainly support the notion that partial withdrawal signs appear in alcoholics who have been drinking for a very short period of time. Recovery function determinations obtained 10 h after alcohol discontinuation indicate enhanced excitability of the somatosensory cortex even after one day of drinking. Our observations are quite consistent with those of Mello and Mendelson (1969) who reported the occurrence of partial withdrawal signs in subjects who had been drinking small amounts of alcohol. Similar results have been obtained with animals after a single dose of ethanol.

McQuarrie and Fingl (1958) have shown decreased seizure thresholds in mice eight hours after a single dose of ethanol. Recently, Goldstein (1972) reported that in mice withdrawal signs occurred at about seven hours after a single ethanol injection. She observed that the severity of withdrawal signs was related to the dose injected. Freund and Walker (1971) have demonstrated that seven hours after withdrawal from alcohol, mice are more susceptible to audiogenic seizures.

A recent study by Bergamasco (1966) demonstrated changes in recovery function due to the administration of cardiazol, a potent sti-

mulant. He reported that the recovery cycle values of the visual cortex of humans during cardiazol treatment, when compared with those of the same subjects in baseline conditions, indicate a substantial increase in the cortical excitability cycle. It was concluded that cardiazol increases cortical excitability by predisposing the cortex to respond to more frequent sensory stimuli by shortening the duration of the recovery cycle. Similarly, our data show a substantial decrease in the duration of the recovery cycle during periods of partial and total withdrawal. This change in the recovery cycle is indicative of cortical hyperexcitability which increases during periods of partial withdrawal following intensive drinking. The exact nature of the time effect of a hyperexcitability cycle in alcoholics has not yet been ascertained, although our data suggest that it reaches a peak approximately 34 h after the last drink and does not return to baseline levels until 58 h subsequent to withdrawal from alcohol. Some clinical observations (Victor, 1970; Gross *et al.*, in press) have indicated that the severity of alcohol withdrawal symptoms is directly related to the severity of the immediately preceding drinking binge. A number of animal experiments (McQuarrie and Fingl, 1958; Freund, 1969; Gibbins *et al.*, 1971; Ellis and Pick, 1971; Goldstein, 1972) have demonstrated that withdrawal reactions are dose-related.

Our present data support the hypothesis that the development of withdrawal symptomatology occurs early in the drinking bout. Furthermore, we observed an increase in central nervous system excitability 10 h subsequent to the last drink, when the blood alcohol level was still elevated. A similar observation has been reported by Goldstein (1972) who found that her mice "could be simultaneously intoxicated and in the early stages of the withdrawal reaction".

Our findings support the hypothesis that partial withdrawal in man is manifested by an increase in brain hyperexcitability which occurs subsequent to depression of the central nervous system by alcohol.

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References

Bergamasco, B.: Excitability cycle of the visual cortex in normal subjects during psychosensory rest and cardiazolic activation. Brain Res. **2**, 51—60 (1966)

Branchey, M., Rauscher, G., Kissin, B.: Modifications in the response to alcohol following the establishment of physical dependence. Psychopharmacologia (Berl.) **22**, 314—322 (1971)

Ellis, F. W., Pick, J. R.: Dose and time dependent relationships in ethanol induced withdrawal reactions. Fed. Proc. **30**, 568 (1971)

Freund, G.: Alcohol withdrawal syndrome in mice. Arch. Neurol. (Chic.) **21**, 315—320 (1969)

Freund, G., Walker, D. W.: Impairment of avoidance learning by prolonged ethanol consumption in mice. J. Pharmacol. exp. Ther. **179**, 284—292 (1971)

Gartside, I. B., Lippold, O. C., Meldrum. B. S.: The evoked cortical somatosensory response in normal man and its modification by oral lithium carbonate. Electroenceph. clin. Neurophysiol. **20**, 382—390 (1966)

Gibbins, R. J., Kalant, H., LeBlanc, E. E., Clark, J. W.: The effects of chronic administration of ethanol on startle thresholds in rats. Psychopharmacologia (Berl.) **19**, 95—104 (1971)

Goldstein, D.: Relationship of alcohol dose to intensity of withdrawal signs in mice. J. Pharmacol. exp. Ther. **180**, 203—215 (1972)

Gross, M. M., Lewis, E., Hastey, J.: Acute alcohol withdrawal syndrome. In: The Biology of alcoholism. B. Kissin and H. Begleiter, Eds., Vol. 3. New York: Plenum Press (in press)

Isbell, H., Fraser, H. F., Wikler, A., Belleville, R. E., Eisenman, A. J.: An experimental study of the etiology of "rum fits" and delirium tremens. Quart. J. Stud. Alcohol **16**, 1—33 (1955)

LeBlanc, E. A., Kalant, H., Gibbins, R. J., Berman, N. D.: Acquisition and loss of tolerance to ethanol by the rat. J. Pharmacol. exp. Ther. **168**, 244—250 (1969)

McQuarrie, D. G., Fingl, E.: Effects of single doses and chronic administration of ethanol on experimental seizures in mice. J. Pharmacol. exp. Ther. **124**, 264—271 (1958)

Mello, N. K., Mendelson, J. H.: Alterations in states of consciousness associated with chronic ingestion of alcohol. In: Neurological aspects of psychopathology, J. Zubin and C. Shagass, Eds., pp. 183—229. New York: Grune and Stratton 1969

Mendelson, J. J.: (Ed.) Experimentally induced chronic intoxication and withdrawal in alcoholics. Quart. J. Stud. Alcohol, Suppl. No. 2 (1964)

Mendelson, J. J., Stein, S., McGuire, M. T.: Comparative psychophysiological studies of alcoholic and nonalcoholic subjects undergoing experimentally induced ethanol intoxication. Psychosom. Med. **28**, 1—12 (1966)

Seevers, M. H., Deneau, G. A.: Physiological aspects of tolerance and physical dependence. In: Physiological Pharmacology, W. S. Root and F. G. Hoffman, Eds. New York: Academic Press 1963

Shagass, C.: Evoked brain potentials in Psychiatry, p. 275. New York: Plenum Press 1972

Shagass, C., Schwartz, M.: Reactivity cycle of somatosensory cortex in humans with and without psychiatric disorder. Science **134**, 1757—1759 (1961)

Victor, M., Adams, R. D.: Effects of alcohol on the nervous system. In: Metabolic and toxic diseases of the nervous system, H. H. Merritt and C. C. Hare, Eds., pp. 526—573. Baltimore: Williams and Wilkins 1953

Victor, M.: The alcohol withdrawal syndrome. Postgrad. Med. **47**, 68—72 (1970)

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