Pharmacology Biochemistry & Behavior, Vol. 25, pp. 889–895, 1986. © Ankho International Inc. Printed in the U.S.A. 0091-3057/86 $3.00 + .00

EEG Alpha Activity Increases During Transient Episodes of Ethanol-Induced Euphoria

SCOTT E. LUKAS,*†[1] JACK H. MENDELSON,*† RICHARD A. BENEDIKT* AND BRUCE JONES*

**Alcohol and Drug Abuse Research Center, McLean Hospital, 115 Mill Street, Belmont, MA 02178 and †Department of Psychiatry, Harvard Medical School, Boston, MA*

Received 15 April 1986

LUKAS, S. E., J. H. MENDELSON, R. A. BENEDIKT AND B. JONES. *EEG alpha activity increases during transient episodes of ethanol-induced euphoria.* PHARMACOL BIOCHEM BEHAV **25**(4) 889–895, 1986.—The effects of acute ethanol administration were studied in 18 men to determine the electroencephalographic (EEG) correlates of ethanol-induced behavioral changes. Subjects were instructed to operate an instrumental device to indicate changes in their subjective mood state while EEG activity and plasma ethanol levels were continuously measured. Three groups of 6 subjects consumed either placebo, 0.347 g/kg ethanol or 0.695 g/kg ethanol over a 15 min period. EEG and behavioral changes were directly correlated with plasma ethanol levels during the ascending limb of the plasma ethanol curve. Theta EEG activity increased proportionally as plasma ethanol levels increased during the 2 hr recording session. Alpha EEG activity increased during the first hour and then returned to control levels. The increased alpha activity was most prominent when subjects reported feeling intense pleasure or euphoria. Power spectral analysis of discrete samples of EEG activity revealed that transient increases in alpha activity paralleled the onset of ethanol-induced euphoria. These data suggest that ethanol-induced behavioral effects are associated with discrete changes in brain electrical activity.

Electroencephalogram (EEG) Ethanol Plasma ethanol levels Ethanol-induced behavior Euphoria Human subjects

THE principal effects of acute ethanol administration on the adult human EEG are an increase in voltage and a slowing of the predominant frequency (cf. [5, 9, 10, 13]). Ethanol also produces numerous behavioral effects ranging from increased alertness to relaxation and a state of well-being or euphoria [4, 14, 33, 35, 40]. Furthermore, these ethanol-induced EEG [9, 15, 30] and behavioral [3, 11, 22] effects occur as plasma ethanol levels are rising.

EEG correlates of the ethanol-induced changes in subjective mood states have been more difficult to establish. The early studies of Engel and associates [12,13] suggested that EEG slowing was related to intoxication and reduced levels of consciousness after ethanol administration, but was unrelated to changes in subjective mood states. Davis *et al.* [9] reported only modest EEG changes in spite of gross alterations in mood and behavior after acute ethanol administration. Thus, direct associations between ethanol-induced changes in CNS activity and behavioral responses are tenable at best [5].

The reason for the lack of direct concordance between EEG activity and subjective mood states may be related to methods for obtaining behavioral measures of drug effects. Typically, measures of ethanol-induced behavioral changes are obtained using checklists or rating scales. However, the spontaneous EEG is very sensitive to movement artifacts as well as changes in levels of alertness when individuals complete questionnaires or perform psychomotor tasks [25,32].

The aim of the present study was to determine the EEG correlates of ethanol-induced intoxication. A non-verbal instrumental device was used to record changes in subjective mood states during concurrent measurement of EEG activity and plasma ethanol levels.

METHOD

Subjects

Eighteen healthy adult male volunteers (57–98 kg) between the ages of 21 and 35 years were recruited via newspaper advertisements and provided informed consent for participation in this study. Subjects were examined by a specialist in internal medicine and only those with normal physical examinations, medical and mental health histories and blood hemogram and chemistry studies were admitted to the study. Urine specimens were screened for psychoactive drugs and all results were negative. No subject had a history

[1]Requests for reprints should be addressed to Scott E. Lukas, Ph.D., Alcohol and Drug Abuse Research Center, Harvard Medical School-McLean Hospital, 115 Mill Street, Belmont, MA 02178.

of drug or ethanol abuse, but all subjects were social drinkers who, on the average, consumed the equivalent of 3 beers per week.

Pollack *et al.* [34] showed that men with positive family histories for alcoholism experienced greater increases in EEG slow alpha and greater decreases in fast alpha activity after receiving ethanol than men with no family history of alcoholism. After the double-blind of the present study was broken we found that only two subjects had a positive family history for alcoholism; one had received placebo, and the other received low-dose ethanol.

Experimental Design and Setting

Effects of two doses of ethanol were compared with placebo in a group design (n=6 per group) under randomized double-blind conditions. The studies were conducted within the context of a multidisciplinary program designed to assess EEG, physiologic, endocrine and behavioral responses following acute ethanol administration. Results obtained using the instrumental device were previously validated and compared with verbal reports of subjective mood states [23].

Subjects were told that they could receive either "placebo, a low dose of alcohol (about 1 shot) or a high dose of alcohol (about 3 shots)." Six subjects received placebo (350 ml of concentrated grapefruit juice plus 3 ml of ethanol "primer" as described below), six subjects received 0.347 g/kg of ethanol (1.1 ml/kg of 80 proof vodka in 350 ml of fruit juice) and six subjects received 0.695 g/kg of ethanol (2.2 ml/kg of 80 proof vodka in 350 ml of fruit juice).

Studies were conducted in an electrically shielded, sound-and-light-attenuated double-walled chamber (IAC, Bronx, NY). The chamber was equipped with a wired intercom and a one-way glass window for maintaining auditory and visual contact with the subjects. Subjects sat in a comfortable reclining chair and were instructed to relax and keep their eyes closed, but to remain awake.

Electrophysiologic Recording Procedures

Electroencephalographic and physiologic activity were recorded on a Model 78D polygraph (Grass Instrument Co., Quincy, MA). Scalp EEG electrodes (C3, C4, P3 and P4) were referenced to linked earlobes and were applied using the International 10–20 System [17]. Temporalis muscle electrodes were used to record muscle tension, a Grass TC-1 thermocouple electrode was attached to the subject's nostril via a plastic clip to record respiratory rate and a Grass PTTL-F photoelectric transducer was attached to a finger to record the subject's pulse. The EEG activity was also recorded on FM magnetic tape for off-line power spectral analysis using a Pathfinder Signal Averaging Microprocessor (Nicolet Instrument Co., Madison, WI). A digital time-code was also recorded on one channel of the magnetic tape to facilitate identification of specific epochs of EEG activity during off-line computerized power spectral analysis.

Blood Sampling Procedures

Blood samples for analysis of integrative plasma ethanol concentrations were withdrawn continuously during the entire study. A 183 cm Kowarski-Cormed Thromboresistant Blood Withdrawal Butterfly Needle and Tubing Set (Cormed Inc., Medina, NY) was used for blood sampling. The extra long length was necessary so that blood could be drawn from outside the chamber without disturbing the subject. The tubing was attached to a 10 ml syringe mounted on a withdrawal syringe pump (Harvard Apparatus, Cambridge, MA) and adjusted to withdraw blood at a rate of 1 ml/min; syringes were changed every 5 min. Plasma samples were immediately prepared and frozen for subsequent ethanol concentration analysis by the spectrophotometric method of Leric *et al.* [19].

Behavioral Measures of Subjective Mood States

A custom-designed manipulandum resembling a joystick device was placed next to the subject's left hand [24]. Movement of the joystick produced a corresponding deflection of an event pen on the polygraph. A button located on the top of the joystick activated a second event pen. The joystick could be moved either forward, backward, or to one side. The joystick was spring-loaded so that it returned to the center position once it was released. Less than 1 Newton of force was required to move the joystick to one of the three different positions.

All subjects were read the following instructions regarding the definition of ethanol-related effects: "You may use any of the following terms to describe alcohol effects or intoxication: giddy, light-headed, buzz-on, high, drunk, or euphoria." Subjects were then instructed to operate the joystick as follows: Forward—"when you feel intoxicated or under the influence of alcohol"; Side—"when you feel that these effects are getting stronger"; Backward—"when the alcohol effects disappear"; Button—"when you experience a feeling of intense well-being or euphoria." Self-reports of intoxication were obtained from the subjects with both an instrumental response and a questionnaire. A previous study comparing instrumental and verbal responses reported that dose-related ethanol-induced changes in mood states were detected using an instrumental response but not with the self-rating questionnaire [23]. Consequently, only data obtained with the instrumental device will be presented here.

Ethanol Administration

Placebo and drug solutions were placed in an inverted IV bottle and attached to a Masterflex peristaltic pump (Cole Parmer Co., Chicago, IL). Tubing from the pump entered through the wall of the experimental chamber. A disposable mouthpiece was attached to the end of the tubing and was supported by a flexible metal arm located near the subject's mouth. For all three treatments (two doses of ethanol and placebo) a 10 ml reservoir located between the pump and the subject's mouthpiece was filled with 3 ml of vodka (i.e., "primer") and 7 ml of juice to provide a strong initial taste of ethanol. This procedure for disguising the solution's taste has proven useful as an effective ethanol placebo control. The small amount of ethanol in the placebo solution does not produce any measurable plasma ethanol levels [27].

Procedure

Baseline EEG, physiologic and behavioral data were recorded during the first 30 min of the study. During this control period subjects were asked to move the joystick and press the button while the EEG was observed for movement-related artifacts. The EEG during these responses was analyzed as described below. After the 30 min baseline period, the subject was instructed to place the drinking tube mouthpiece comfortably into his mouth and the peristaltic pump was activated to deliver 350 ml of solution

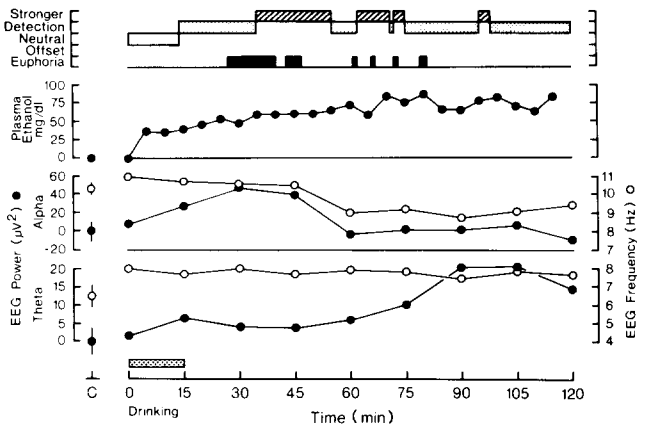

FIG. 1. Time course of behavioral changes, plasma ethanol levels and EEG activity in one subject after drinking 0.695 g/kg ethanol. Behavioral measures were obtained continuously using a joystick device. Two minute artifact-free EEG epochs were analyzed every 15 min using power spectral analysis techniques. Control values represent mean±SD of five 2-min samples obtained during the 30 min control session.

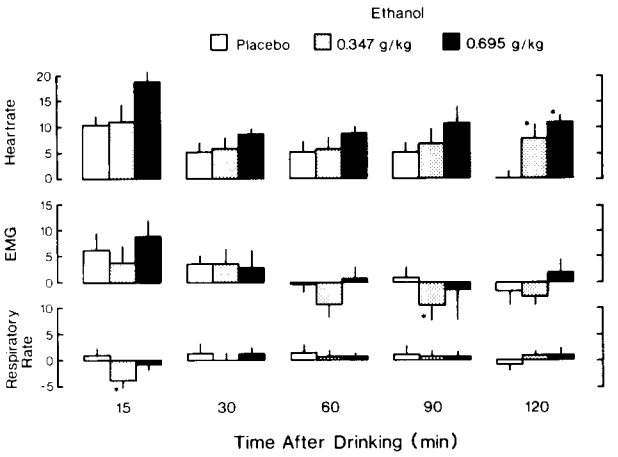

FIG. 2. Time course of heart rate, muscle tension (EMG) and respiratory rate changes after drinking placebo, low-dose ethanol or high-dose ethanol. Values represent means±SE of the change from baseline control values for 6 subjects. *Denotes values significantly different from placebo values at $p<0.05$.

over a 15 min time period. Continuous measures of EEG, physiologic and behavioral responses and blood samples were obtained for the next 2 hours.

Data Analysis

Pulse rate, muscle tension and respiratory rate were measured each min during the first 60 min after drinking and at 5-min intervals for the subsequent 60 min. Movements of the joystick indicating ethanol detection and episodes of euphoria were directly recorded on the polygraph. Discrete, 2 min artifact-free epochs of EEG activity were selected every 15 min for power spectral analysis using Frequency Analysis Software developed by Nicolet Instrument Co. The process digitized the analog waves at a rate of 256 Hz, performed a Fast Fourier Transformation on the sample and then generated a compressed spectral array representing EEG power as a function of frequency. The corresponding power (uV^2/Hz) and peak frequency (Hz) in the 0.25–4 Hz, 4–8 Hz, 8–13 Hz and 13–30 Hz were quantified and printed for 20 sec epochs of EEG activity.

Statistical analysis was performed on an Apple IIe microcomputer using software developed by Human Systems Dynamics (Northridge, CA). Analysis of variance with repeated measures followed by Dunnett's significant difference test, linear regression, and correlation and covariance tests were utilized as necessary. Tests for parallelism were conducted using the method of Tallarida and Murray [37].

RESULTS

Acute ethanol administration produced obvious changes in behavioral states. These effects were not accompanied by gross changes in physiological measures, but were related to alterations in EEG activity and plasma ethanol levels.

Figure 1 shows the temporal relationship between the behavioral responses, plasma ethanol levels and EEG activity of one subject who had received 0.695 g/kg of ethanol. This subject detected ethanol effects 14 min after drinking had begun when his plasma ethanol level was about 42 mg/dl. The subject subsequently alternated between a mildly and strongly intoxicated state for the rest of the recording session. Between 25 and 80 min after the onset of drinking, the subject experienced multiple paroxysmal episodes of euphoria. Five out of six subjects that received this dose of ethanol reported euphoria while only one subject in the 0.347 g/kg dose group reported euphoria—and this was a single episode that lasted 70 sec. None of the subjects who received placebo reported euphoria. The duration of behavioral effects (mean±s.d.) following placebo, low-dose ethanol and high-dose ethanol was 41.6±8.8, 96.8±7.1 and 103.2±8.2 minutes, respectively.

Changes in theta and alpha EEG activity also followed a particular time course. Alpha energy increased and then returned to control levels by 60 min after drinking. The predominant peak frequency in the alpha band decreased from 11 Hz to 9 Hz in three of the six subjects who received 0.695 g/kg of ethanol. The other three subjects had a relatively slow (8–9 Hz) control alpha frequency which remained unchanged after ethanol administration (data not shown). No changes in peak theta frequency occurred, but theta energy gradually increased during the course of the recording session.

Figure 2 shows the time course of effects of ethanol on pulse, muscle tension and respiratory rate for all subjects. Except for four exceptions (indicated by asterisks) ethanol-induced changes in physiological activity were not significantly different from placebo-treated subjects.

Figure 3 depicts the temporal pattern of EEG changes from the P4 lead in theta (4–8 Hz) and alpha (8–13 Hz) power, plasma ethanol levels, and the incidence of episodes of euphoria for all ethanol-treated subjects. No changes in either the theta or alpha EEG band occurred during the recording session after placebo administration (data not shown). The 0.347 g/kg dose of ethanol did not affect alpha power but significantly increased power in the theta band 60–90 min after drinking began. The 0.695 g/kg dose of ethanol produced significant increases in theta power which paralleled the plasma ethanol curve. This relationship was

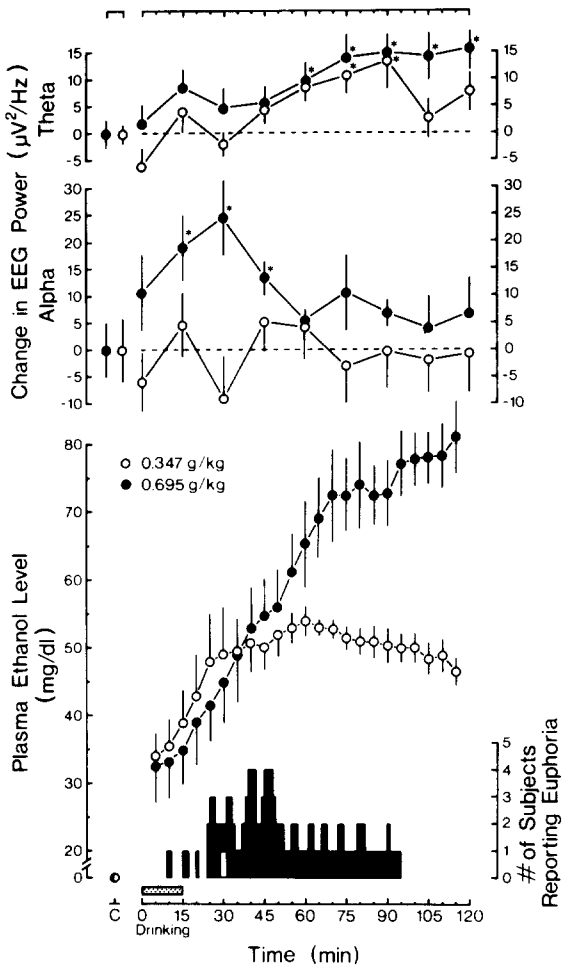

FIG. 3. Time course of changes in theta (4–8 Hz) and alpha (8–13 Hz) EEG activity, plasma ethanol levels and reported episodes of euphoria after low dose (○) and high dose (●) ethanol administration. Control EEG data was obtained as described in Fig. 1. Values represent means±SE for 6 subjects except for the reported episodes of euphoria which are plotted as actual episodes. The single episode produced by low dose ethanol is indicated by the small white block at 30–31 min.

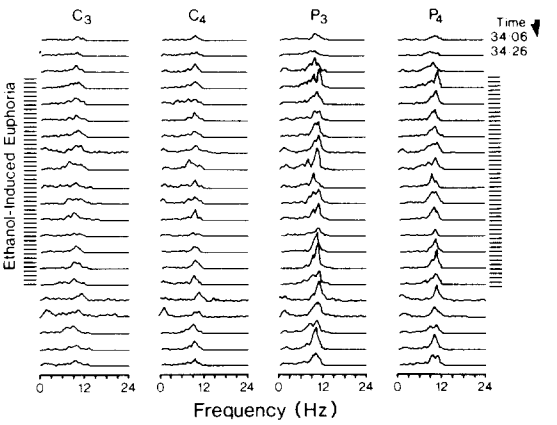

FIG. 4. Individual power spectral plots from one subject during high-dose ethanol-induced euphoria. Each plot represents 20 sec of EEG activity from 4 electrode sites. Shaded area indicates the duration of euphoria as indicated by pushing the button on the joystick device. Time elapses from top to bottom.

confirmed by linear regression analysis ($y=0.34x-11.70$; $r^2=0.93$) and the correlation coefficient (r) was calculated to be 0.97. Alpha power was significantly increased by high dose ethanol at 15, 30 and 45 min after drinking while the low dose ethanol did not alter alpha power. Alpha power declined to control levels by 45 min after subjects had finished consuming high-dose ethanol. The incidence of euphoria episodes paralleled this bimodal change in alpha power ($y=0.49x+5.61$; $r^2=0.89$) and was highly correlated ($r=0.95$). Only a single short episode of euphoria was reported by one subject who had received low dose ethanol. While the absolute plasma ethanol levels after both doses were not significantly different up to 45 min after drinking began, the slopes were significantly different during the 25–50 min period when the greatest incidence of reported euphoria occurred. The slopes and 95% confidence intervals for high dose- and low dose-induced plasma ethanol curves were 0.599 (0.432–0.767) and 0.153 (0.091–0.214) mg/dl/min, respectively, which were not parallel (calculated $t(8)=6.943$, $p<0.01$).

The electrophysiological correlates of ethanol-induced euphoria were more precisely measured by subjecting 20 sec epochs of EEG activity to power spectral analysis. Figure 4 shows a representative series of power spectra from one subject during euphoria (shaded area) 34 min after consuming 0.695 g/kg of ethanol. Little or no increases occurred in the central leads C3 and C4, but pronounced alpha activity appeared during the onset of euphoria in leads P3 and P4. The increased alpha activity persisted 1–2 min after the joystick was released. This increase in alpha power was not observed during simulated, control joystick responses obtained during the first 30 min of the study (data not shown).

Group EEG data from leads C4 and P4 recorded before, during the first 40 seconds, and after reported episodes of euphoria are shown in Fig. 5. Data are from all episodes reported by the 5 subjects who reported euphoria. Each histogram represents 20 seconds of EEG activity and is divided into the amount of power in the 0.25–4, 4–8, 8–13 and 13–30 Hz frequency bands. Alpha power in lead P4 was significantly increased during euphoria and returned to pre-euphoria levels after the joystick button was released.

DISCUSSION

Acute administration of ethanol produced EEG and behavioral changes which were most prominent during the ascending limb of the plasma ethanol curve. The EEG changes were limited to the theta and alpha bands and were positively correlated with plasma ethanol levels and discrete episodes of euphoria.

Exhilaration, elation or euphoria after consuming ethanol have been measured with questionnaires and described as increased talkativeness, raised spirits, higher pitched voice and increased feelings of contentment and relaxation [1, 2, 6, 16, 18, 33, 40]. In the present study, subjects were required to move the instrumental device when they detected ethanol effects and to signal euphoria by depressing a button located on top of the joystick. Thus, they could report detection of

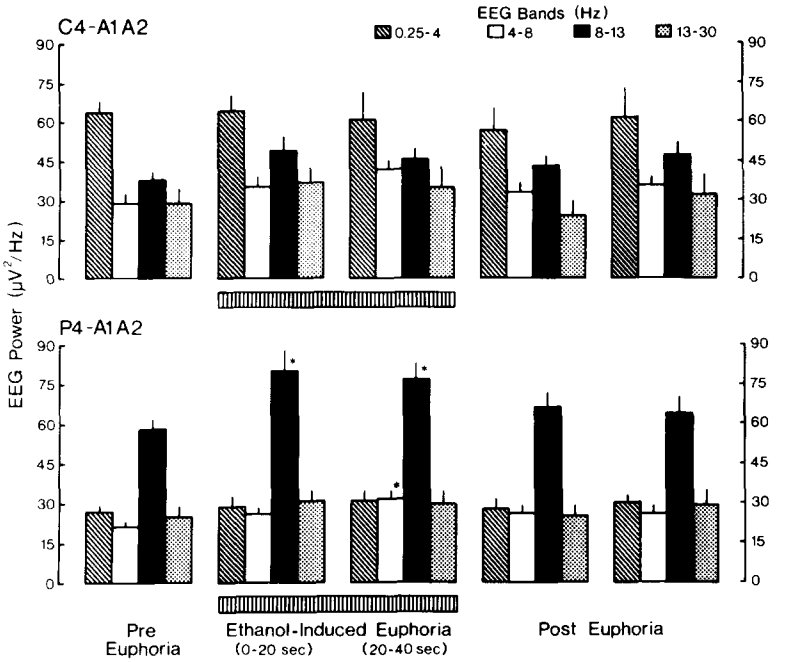

FIG. 5. Group delta (0.25–4 Hz), theta (4–8 Hz), alpha (8–13 Hz) and beta (13–30 Hz) EEG activity 20 seconds before, the first 40 seconds of euphoria and 40 seconds after high dose ethanol-induced euphoria (indicated by vertical bar). Data represent mean ± SE of 20 second epochs of EEG activity recorded from C4 (top 5 histograms) and P4 (bottom 5 histograms) electrode sites. *Denotes values significantly different from pre-euphoria values at $p<0.05$.

ethanol effects independently from experiencing euphoria. However, no subject reported euphoria without first detecting an ethanol effect.

Heart rate and muscle tension increased after both ethanol and placebo intake. These measures returned to baseline levels within 30 minutes after drinking. Except for the decrease in respiratory rate while drinking the low dose of ethanol, significant differences in these physiological parameters occurred during the last 30 minutes of the session. It is unlikely that these changes contributed to the EEG or behavioral responses to ethanol.

Previous studies have demonstrated that ethanol produces increased alpha activity and a slowing of the alpha frequency [9, 10, 13]. There is considerable variation in EEG activity following acute ethanol administration, but this may be associated with different degrees of tonic inhibition of the desynchronizing ascending reticular activating system resulting in different baseline EEG frequencies. This explanation evolved from the work of Engel and Rosenbaum [13] and Varga and Nagy [39] who showed that ethanol produced a slower, more "normal" rhythm in subjects with relatively fast EEG activity. These authors have argued that the relative change in EEG activity is more important than the absolute levels.

Naitoh and Docter [29] hypothesized that individuals drink alcohol to become more alert and sociable. They noted that these behavioral changes were accompanied by increased alpha activity and alpha slowing. This interpretation, however, is not consistent with the established relationship between increased levels of alertness and decreased or "blocked" alpha activity [25,32]. There are reports that ethanol also induces EEG activation (i.e., low voltage, fast-frequency) particularly after lower doses or during the early ascending limb of the plasma ethanol curve [21,39].

These discrepancies in previous reports of ethanol's EEG effects may be clarified from the results obtained in the present study. Theta power increased gradually as plasma ethanol levels rose. This progression of increased theta activity may have been perceived as a slowing of alpha or overall frequency when the raw EEG records were visually analyzed in many previous studies. In the present study, power spectral analysis of discrete EEG epochs revealed that the predominant alpha frequency was unaffected by 0.347 g/kg of ethanol. The higher dose of ethanol slowed the predominant alpha frequency only in those individuals who began the study with a relatively faster alpha frequency during the control period. Yet, an increase in spontaneous EEG alpha power occurred during the first 60 minutes after drinking high dose ethanol which was when most episodes of euphoria were reported. This observed increase in alpha activity is consistent with a more relaxed but awake state typical of the subjects' behavior in the isolated chamber. It is likely that alterations in neuronal function induced by ethanol influences changes in behavior and spontaneous EEG activity concurrently. Thus, fluctuations in behavioral and subjective mood states must be measured continuously to detect correlations with brain wave activity.

In addition to the gradual increase in spontaneous alpha activity after 0.695 g/kg of ethanol, the discrete episodes of euphoria were associated with transient increases in alpha activity which exceeded the already elevated alpha levels. This is the first demonstration of such a relationship between

brain electrical activity and ethanol-induced euphoria. The discovery of this relationship was possible because subjects reported euphoria with a non-verbal instrumental response that required minimal muscle activity. The relatively brief duration of episodes of euphoria is consistent with the notion that substances that produce relatively rapid transitions between behavioral states are efficacious reinforcers [26].

Episodes of euphoria were most often reported 25–50 min after the high dose of ethanol. The appearance of euphoria was clearly related to a minimal plasma ethanol level that was rapidly rising (Fig. 3). However, the relatively brief nature of the actual euphoric episodes is difficult to explain on the basis of changes in plasma ethanol levels alone. The present study employed an integrative blood sampling technique which attenuates or smooths differences between consecutive 5 min samples; this procedure makes it impossible to determine if the 1–2 min episodes of euphoria were temporally related to rapid, but small, transitions in plasma ethanol levels. This does not preclude the possibility that rapidly changing levels of ethanol in the brain produced the observed changes in behavioral state and on brain electrical activity. It is likely that euphoria results when a threshold plasma ethanol level is attained at a sufficiently rapid rate. This is consistent with the finding that all subjects who received low-dose ethanol developed plasma ethanol levels in excess of 45 mg/dl; but the slope was only 0.15 mg/dl/min versus 0.6 mg/dl/min for the high-dose group.

An alternative explanation for the rapid appearance of euphoria may be that acetaldehyde or tetrahydroisoquinolines (TIQ) may have produced the EEG and behavioral changes. These products appear very soon after ethanol administration to *in vitro* preparations [8, 20, 31], but the evidence for *in vivo* formation is sparse [36,38]. In rats, acute, but not chronic IV administration of acetaldehyde induces EEG changes similar to those produced by ethanol [28]. Thus, while there is no conclusive evidence to support the theory that ethanol metabolites or condensation products produce EEG and behavioral effects, definitive studies have not been conducted to completely rule out this possibility.

In conclusion, acute administration of ethanol produces multiple, short episodes of euphoria during the ascending limb of the plasma ethanol curve. Further, these paroxysmal episodes of instrumentally-reported euphoria were associated with transient increases in EEG alpha activity—a rhythm normally associated with a free-floating, relaxed state. This study is the first report of an association between specific ethanol-induced changes in mood state and spontaneous electrophysiological activity suggesting that enhanced alpha activity is related, at some level, to drug-induced elevated mood states.

ACKNOWLEDGEMENTS

This work was supported by Grant AA 06252 from the National Institute on Alcohol Abuse and Alcoholism and Research Scientist Award DA 00064 (Jack H. Mendelson, M.D.) from the National Institute on Drug Abuse. The authors thank A. S. T. Skupny for conducting the plasma ethanol assays, S. Palmieri and C. de Marneffe for data analysis and R. Head for secretarial assistance

REFERENCES

1. Abramson, H. A. The effect of alcohol on the personality inventory (Minnesota): A preliminary report. *Psychosom Med* **7:** 184–185, 1945.
2. Alha, A. R. Blood alcohol and clinical inebriation in Finnish men. *Ann Acad Sci Fenn [A]* **26:** 1–92, 1951.
3. Babor, T. F., S. Berglas, J. H. Mendelson, J. Ellingboe and K. Miller. Alcohol, affect, and the disinhibition of verbal behavior. *Psychopharmacology (Berlin)* **80:** 53–60, 1983.
4. Battig, K. and H. Fischer. Personlichkeitsmerkmale, subjektives Selbstempfinden und psychomotorische Leistung unter Alkoholeinfluss bei jungen, nicht alkoholgewohnten Individuen. [Personality characteristics, subjective experience and psychomotor performance of young, non-habituated subjects under the influence of alcohol.] *Z Praventivmed* **10:** 386–396, 1965.
5. Begleiter, H. and A. Platz. The effects of alcohol on the central nervous system in humans. In: *The Biology of Alcoholism*, vol. 2, edited by B. Kissin and H. Begleiter. New York: Plenum Press, 1972, pp. 293–343.
6. Bjerver, K. and L. Goldberg. Effects of alcohol ingestion on driving ability. *Q J Stud Alcohol* **11:** 1–30, 1950.
7. Cohen, G. A role for tetrahydroisoquinoline alkaloids as false adrenergic neurotransmitters in alcoholism. In: *Advances in Experimental Medicine and Biology, Vol 35, Alcohol Intoxication and Withdrawal Experimental Studies*, edited by M. M. Gross. New York: Plenum Press, 1973, pp. 33–44.
8. Cohen, G. Alkaloid products in the metabolism of alcohol and biogenic amines. *Biochem Pharmacol* **25:** 1123–1128, 1976.
9. Davis, P. A., F. A. Gibbs, H. Davis, W. W. Jetter and L. S. Trowbridge. The effects of alcohol upon the electroencephalogram (brain waves). *Q J Stud Alcohol* **1:** 626–637, 1941.
10. Docter, R. F., P. Naitoh and J. C. Smith. Electroencephalographic changes and vigilance behavior during experimentally induced intoxication with alcoholic subjects. *Psychosom Med* **28:** 605–615, 1966.
11. Ekman, G., M. Frankenhaeuser, L. Goldberg, R. Hagdahl and A.-L. Myrsten. Subjective and objective effects of alcohol as functions of dosage and time. *Psychopharmacologia* **6:** 399–409, 1964.
12. Engel, G. L. and M. Rosenbaum. Studies of the electroencephalogram in acute alcoholic intoxication. *Proc Cent Soc Clin Res* **17:** 62–63, 1944.
13. Engel, G. L. and M. Rosenbaum. Delerium III. Electroencephalographic changes associated with acute alcohol intoxication. *Arch Neurol Psychiatry* **53:** 44–50, 1945.
14. Engel, G. L., J. P. Webb and E. B. Ferris. Quantitative electroencephalographic studies of anoxia in humans: comparison with acute alcoholic intoxication and hypoglycemia. *J Clin Invest* **24:** 691–697, 1945.
15. Holmberg, G. and S. Martens. Electroencephalographic changes in man correlated with blood alcohol concentration and some other conditions following standardized ingestion of alcohol. *Q J Stud Alcohol* **16:** 411–424, 1955.
16. Howells, D. E. Nystagmus as a physical sign in alcoholic intoxication. *Br Med J* **1:** 1405–1406, 1956.
17. Jasper, H. H. The 10-20 electrode system of the International Federation. *Electroencephalogr Clin Neurophysiol* **10:** 371–375, 1958.
18. King, A. R. Tunnel vision. *Q J Stud Alcohol* **4:** 362–367, 1943.

19. Leric, H., J.-C. Kaplan and G. Broun. Dosage enzematic de l'alcool sanguin par micromethode colorimetrique [A colorimetric micromethod for the enzymatic assay of ethanol in blood]. *Clin Chim Acta* **29:** 523–528, 1970.
20. Locke, S. D., D. Dembiec and G. Cohen. In vivo inhibition of neuronal uptake of a dopamine-derived tetrahydroisoquinoline (TIQ) alkaloid by cocaine and by desmethylimipramine (DMI). *Fed Proc* **32:** 526, 1973.
21. Lolli, G., R. Nencini and R. Misiti. Effects of two alcoholic beverages on the electroencephalographic and electromyographic tracings of healthy men. *Q J Stud Alcohol* **25:** 451–458, 1964.
22. Loomis, T. A. and T. C. West. The influence of alcohol on automobile driving ability: An experimental study for the evaluation of certain medicolegal aspects. *Q J Stud Alcohol* **19:** 30–46, 1958.
23. Lukas, S. E., J. H. Mendelson and R. A. Benedikt. Instrumental analysis of ethanol-induced intoxication in human males. *Psychopharmacology (Berlin)* **89:** 8–13, 1986.
24. Lukas, S. E., J. H. Mendelson, R. A. Benedikt and B. Jones. EEG, physiologic and behavioral effects of ethanol administration. In: *Problems of Drug Dependence 1985, NIDA Research Monograph*, edited by L. S. Harris. Washington, DC: U.S. Government Printing Office, 1986, pp. 209–214.
25. Matousek, M. and I. Petersen. A method for assessing alertness fluctuations from EEG spectra. *Electroencephalogr Clin Neurophysiol* **55:** 108–113, 1983.
26. Mello, N. K. Stimulus self-administration: Some implications for the prediction of drug abuse liability. In: *Predicting Dependence Liability of Stimulant and Depressant Drugs*, edited by T. Thompson and K. R. Unna. Baltimore: Universtity Park Press, 1977, pp. 243–260.
27. Mendelson, J. H., M. McGuire and N. K. Mello. A new device for administering placebo alcohol. *Alcohol* **1:** 417–419, 1984.
28. Mikeska, J. A. and W. R. Klemm. Evidence against a role of acetaldehyde in electroencephalographic signs of ethanol-induced intoxication. *Science* **203:** 276–279, 1979.
29. Naitoh, P. and R. F. Docter. Electroencephalographic and behavioral correlates of experimentally induced intoxication with alcoholic subjects. Washington, DC: *28th Inter. Congr. Alcohol Alcoholism*, 1968, pp. 76–77.
30. Newman, H. W. The effect of alcohol on the electroencephalogram. *South Stacks Stanford Med Bull* **17:** 55–60, 1959.
31. Osswald, W., J. Polonia and M. A. Polonia. Preparation and pharmacological activity of the condensation product of adrenaline with acetaldehyde. *Naunyn Schmiedebergs Arch Pharmacol* **289:** 275–279, 1975.
32. Otto, E. The effect of instructions influencing the level of alertness on the EEG activity. In: *Mechanisms of Orienting Reaction in Man*, edited by I. Nedecky. Bratislave: Slovak Acad. Sci. Publ. House, 1967, pp. 351–365.
33. Pihkanen, T. A. Neurological and physiological studies on distilled and brewed beverages. *Ann Med Exp Biol Fenn* **35:** Suppl 9, 1–152, 1957.
34. Pollack, V. E., J. Volavka, D. W. Goodwin, S. A. Mednick, W. F. Gabrielli, J. Knop and F. Schulsinger. The EEG after alcohol administration in men at risk for alcoholism. *Arch Gen Psychiatry* **40:** 857–861, 1983.
35. Sargant, W., P. Slater, H. Halstead and M. Glen. Effects of alcohol and sodium amytal on intelligence-test score. *Lancet* **248:** 617–618, 1945.
36. Sippel, H. W. The acetaldehyde content in rat brain during ethanol metabolism. *J Neurochem* **23:** 451–452, 1974.
37. Tallarida, R. J. and R. B. Murray. *Manual of Pharmacologic Calculations*. New York: Springer Verlag, 1981.
38. Turner, A. J., K. M. Baker, S. Algeri, A. Frigerio and S. Garattini. Tetrahydropapaveroline: Formulation in vivo and in vitro in rat brain. *Life Sci* **14:** 2247–2257, 1974.
39. Varga, B. and T. Nagy. Analysis of alpha-rhythms in the electroencephalogram of alcoholics. *Electroencephalogr Clin Neurophysiol* **12:** 933, 1960.
40. Wolff, H. G., J. D. Hardy and H. Goodell. Measurement of the effects on the pain threshold of acetylsalicyclic acid, acetanilid, acetophenetidin, aminopyrine, ethyl alcohol, trichlorethylene, a barbiturate, quinine, ergotamine tartrate and caffeine: An analysis of their relation to the pain experience. *J Clin Invest* **20:** 63–80, 1941.