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Changes in Fixed-Ratio Performance and Blood Alcohol Levels in Monkeys

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Abstract. Three female Bonnet monkeys prepared with indwelling venous catheters were maintained on a fixed-ratio schedule of food reinforcement until response rates were stable. The animals were then intubated with alcohol (5.0 g/kg) 30 min prior to testing. Blood alcohol concentrations (BACs) were determined every 15 min throughout the 90-min session. Each alcohol intubation was separated by 3 days and on the second control day an isocaloric sucrose solution was intubated. The results show that the alcohol-induced response suppression gradually returns to baseline levels after 5 alcohol intubations, and the BACs were concomitantly decreased. The results indicate that the reversibility of alcohol induced behavioral impairments and changes in BACs develop within similar temporal intervals.

Key words: Fixed ratio – Blood alcohol concentration – Alcohol – Tolerance – Monkeys

Among previous reports there has been considerable disagreement as to whether or not recovery of alcohol-induced behavioral changes following repeated alcohol exposure is accompanied by systematic changes in the blood alcohol concentration (BAC). Experimental and clinical evidence indicate that the degree of tolerance observed in alcoholics cannot be accounted for by changes in the BAC (Mendelson and Stein, 1966). Nevertheless, changes in blood alcohol elimination rates are a common feature of acute and chronic alcohol exposures (Pieper and Skeen, 1973) and it has been suggested that an increased rate of alcohol elimination may relate in part to the decrease in behavioral impairment following repeated alcohol exposures (Mendelson et al., 1965). Hogans et al. (1961) have shown that as the blood alcohol level was raised the impairment of avoidance responding in monkeys was correlated with increased signs of central nervous system (CNS) depression evidenced by electroencephalographic measures. However, the authors point out that the daily variation in the concentration of alcohol found in the blood was large, and suggest that the BAC is not an important factor in the changes that occur in behavior. Similarly, clinical studies have shown that the BAC is poorly correlated with the behavioral indices of intoxication (Mirsky et al., 1941).

While the evidence suggests that changes in BAC do not reflect changes in behavior, there are some investigations demonstrating a functional relationship between BAC and memory impairment (Jones and Vega, 1972; Jones, 1973). Further correlations between BAC and CNS activity have been extensively documented (Begleiter and Platz, 1972; Hogans et al., 1961; Mirsky et al., 1941; Salamy and Williams, 1973). In a recent study investigating the effects of alcohol on sensory evoked responses in man (Salamy and Williams, 1973), the amplitude of the response decreased systematically during the rising concentration of alcohol and returned to baseline levels during the falling concentration of alcohol in the blood. The relationship between the blood level of a drug and its pharmacological action has been the subject of many scientific inquiries, but there are still few drugs for which the behavioral effects have been related to the circulating blood level.

Low doses of alcohol (1.0 g/kg) do not affect timing behavior in rats (Sidman, 1955; Sanders and Pilley, 1973) or man (Laties and Weiss, 1962), but a larger dose (1.7 g/kg) shifts the interresponse time distribution of a differential reinforcement of low rate schedule, suggesting a definite effect on timing (San-

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ders and Pilley, 1973). Similarly, various doses of alcohol have been shown to suppress behavior maintained on fixed-ratio schedules (Holloway and Vardiman, 1971). Mello (1971) studied the effects of alcohol on delayed matching to sample in Rhesus monkeys and reported that decreased accuracy was correlated with high BAC. Unfortunately, the procedure did not permit a BAC to be determined during each session, and BACs were determined following the behavioral session. The purpose of the present investigation was to evaluate the effects of repeated alcohol and isocaloric sucrose intubations on schedule-controlled behavior and to examine the relationship between behavioral changes and blood alcohol levels in monkeys.

MATERIALS AND METHODS

Animals. Three experimentally naive female Bonnet monkeys (Macaca Radiata) weighing 3.6, 3.9, and 4.0 kg were individually housed and gradually reduced to 90% of their free feeding weights, at which they were maintained throughout the experiment. During the behavioral testing the monkeys were restrained in a standard BRS/LVE Rhesus chair (Model pc001), which was placed in a BRS/LVE sound-attenuated ventilated cubicle (Model 132-14). Following the behavioral testing the animals were returned to their home cages.

Procedure. Following weight reduction the animals were shaped to press a bar for a 190 mg Noyes banana flavored pellet and allowed to earn 100 reinforcements on a continuous reinforcement schedule (CRF) for two consecutive days. Following CRF training the schedule contingency was changed to a fixed-ratio 5 (FR 5) with a 10-s time-out (TO) following each reinforcement. During the TO all lights were extinguished and responses had no scheduled consequence. The schedule parameters were gradually lengthened until final values were FR 50, TO 1 min. Following 5 days of FR 50, TO 1 min training, a 1-min limited hold (LH) was superimposed on the FR 50 schedule. If the FR 50 was not completed within 1 min the TO was initiated and the FR counter for responses completed returned to zero. Each session lasted 90 min.

Following 40 days of training on this schedule the animals were anesthesized with acepromazine meleate (3 mg/kg/im) and sodium pentobarbital (20.0 mg/kg/i.v.) and under sterile operating conditions implanted with an i.v. indwelling catheter. The catheter, made of silicone tubing (0.025×0.047 ID $\times$ OD inches) was anchored into the external jugular vein and the proximal end passed i.v. into the heart, while the distal end was passed s.c. from the neck to the midline of the back where it exited (Stretch and Gerber, 1970). Immediately following surgery the animals were placed in a close fitting canvas vest to protect the exposed portion of the catheter. After the surgical procedures and a 1-week recovery period, the subjects were tested daily beginning at 1000 h. Each 90-min session was divided into six 15-min segments, and response rates were calculated for each segment. Daily response rate comparisons were made for each 15-min segment, and when the rates varied less than 10% for five consecutive days the experimental phase was begun, in which animals were intubated (without anesthesia) via the nasogastric route with ethanol as a 30% (w/v) solution in tap water (5.0 g/kg) 30 min prior to the daily testing session.

Following the baseline determination, the monkeys were tested for 20 consecutive days as follows: alcohol intubation (5.0 g/kg) on day one, no intubation on day two, isocaloric sucrose intubation on day three, and no intubation on day four. The 4-day sequence was repeated five times. On the first and third days of each 4-day sequence, blood samples (1.0 ml) were drawn from the catheter at 15-min intervals that coincided with the response rate determinations. The portion of the catheter which exited the animal's back was connected to sterile tubing that was passed through a hole in the experimental chamber. This permitted blood samples to be drawn without opening or disturbing the animals. The first 15-min response rate and BAC was determined 45 min after the intubation. The catheter was flushed with sterile saline following each blood sample to insure that each sample would not be contaminated by the previous one, and the saline was removed just prior to the next blood sampling. Sterile disposable syringes were used for each sample to minimize contamination of the catheter. All blood samples were immediately placed in heparinized vacutainers and refrigerated until assayed. The blood was analyzed in a Beckman spectrometer using a Beckman hydrogen lamp. The samples were prepared with Calbiochem Ethyl Alcohol Reagents and analyzed by enzymatic procedures described by Calbiochem (La Jolla, California 92037).

RESULTS

The first graph in Figure 1 shows the mean response rate for the three monkeys for the baseline and alcohol test days. Each point represents the rates of response during the immediately preceding 15-min interval. The mean response rate for the baseline sessions across the five baseline days varied less than 10% from day to day, and each of the six time segments varied less than 15% from day to day. The remaining five functions on graph 1 show the response rate sampled every 15 min throughout the 90-min test session. The first alcohol intubation produced a suppression of the response rate that was negatively correlated ($r = -0.829$) with increased BAC, and at the end of the first session the response rates were near zero. Graph 1 in Figure 1 also shows that the alcohol-induced response suppression gradually diminished across the five intubations, and the response rate did not differ from baseline levels during the fifth alcohol test block ($P < 0.01$ Student's t-test).

The second graph in Figure 1 shows the mean BAC for the three monkeys during the five alcohol test sessions. The figure shows that the high BACs that occurred during the first two alcohol test sessions decreased with repeated intubations. It should be noted that during the second alcohol test session the level of alcohol in the blood for monkeys MB20 and MP31 was lower than the first session. The means for these animals during the first alcohol test session were 255.6 and 299.6 mg/100 ml of blood respectively, whereas the means during the second alcohol test session were 190.8 and 234.8 mg/100 ml blood. Conversely, the BAC at all six intervals of the 90-min session for the third animal (MJ3) was elevated above the level observed during the first session. In both the first and second alcohol test sessions the peak BAC

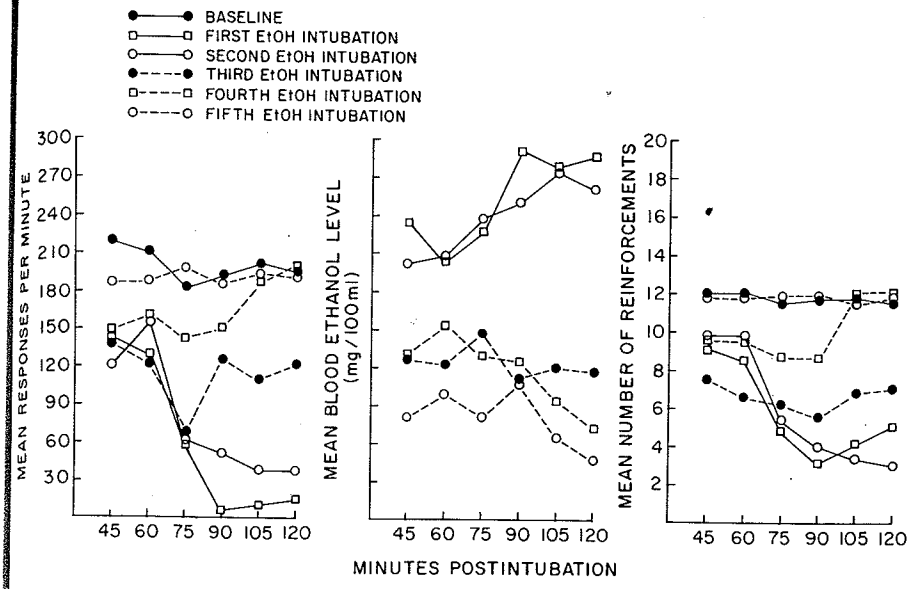

Fig. 1. Mean response rate (graph 1) and BAC (graph 2) as a function of the six 15-min time segments for baseline and alcohol test sessions. Baseline data shows mean of 5-days daty ßrior to beginning of experimental procedure. Graph 3 shows mean number of reinforcements for baseline and alcohol test sessions over time

occurred between 90 and 105 min postintubation, whereas the greatest response suppression occurred 75–90 min following the intubation. However, during the third alcohol test session the BACs were reduced compared to the first two sessions and there was a shift in the peak BAC from 90 or 105 min to 75 min postintubstion. The first two graphs in Figure 1 show that the mean response rate on alcohol test days is positively accelerated with the greatest acceleration occurring during the third or fourth day, whereas the BAC shows a negatively accelerated slope with the largest reduction occurring during the third test day.

The third graph in Figure 1 shows the mean number of reinfrocements for baseline and alcohol test days. Each point represents the number of reinforcements during the immediately preceding 15 min. The figure shows that with repeated alcohol exposure the suppressed food intake returns to baseline levels during the fifth alcohol session, and there was no significant difference between baseline and fifth session food intake ($P < 0.001$ Student's t-test). Similarly, a statistical evaluation of the largest difference between baseline response rates and sucrose test days yielded no significant difference between them ($P < 0.01$ Student's t-test).

DISCUSSION

The results show that the suppressed responding exhibited by all subjects during the first two alcohol test sessions diminished with repeated alcohol administration and that changes in behavior were concominant with changes in BAC. The gradual return of the FR responding to prealcohol levels cannot be accounted for by an increase in training since all animals were brought to stable levels of performance prior to the test phase and there were no major differences between baseline response rates and those obtained during control days.

A major difficulty in studying the effects of alcohol on food-directed behavior is that alcohol has a high caloric content and changes in behavior may result from the caloric rather than the pharmacological properties of alcohol. In this study the suppression of FR performance in the first four alcohol test sessions cannot be accounted for by the caloric value of alcohol because isocaloric sucrose intubations on control days failed to produce any observable change in FR behavior. The blood collection on alcohol test days did not contribute to the response rate suppression since the same blood collection procedure was used on sucrose control days. The possibility that the differential amount of food consumed by the animals during the test session affected the rate of absorption of ethanol cannot be completely eliminated. Food delays the absorption of alcohol, producing a slower rise and lower peak value of blood alcohol. However, the third graph in Figure 1 shows that the maximum number of reinforcements in any single 15-min interval did not exceed 12, which equals 2.28 g of food and only 13.68 g in a total session. Since the animals were intubated 30 min prior to the beginning of the session and were food-deprived, the amount of food eaten during the first 15 min would

seem to have minimal effects on alcohol absorption. Therefore, the suppression of FR performance appears to be a direct result of the pharmacological effects of alcohol and the gradual return of stable response rates may represent tolerance.

While tolerance to ethanol has been repeatedly demonstrated in rats (LeBlanc et al., 1975, 1976), monkeys, and man (Kalant et al., 1971) the relationship between the behavioral changes during repeated exposure to alcohol and changes in BAC has received little experimental attention. The present data demonstrate that in monkeys the duration of alcohol-induced behavioral disruption was correlated with changes in BAC. A previous report (Hogans et al., 1961) suggested that the concentration of alcohol in the blood was not an important factor in the recovery of alcohol-induced behavioral and EEG changes. However, LeBlanc et al. (1975) demonstrated that a reduction of alcohol-induced impairment on a moving belt test at a given blood level on the falling versus the rising amount of the BAC. Since repeated exposure of an organism to alcohol affects the rate of ethanol elimination, it seems reasonable that changes in behavior would functionally be related to BAC (Mendelson and Stein, 1966; Pieper and Skeen, 1973). In the present study the changes in BAC after repeated alcohol administration are similar to the results obtained by Pieper and Skeen (1973). These authors demonstrated that elimination rates increased by a mean of 102% ± 13.3 SE in Rhesus monkeys following chronic administration of a 6.9 g/kg dose. A major difference between the two studies was that in our present experiment a 5.0 g/kg dose of alcohol was administered every fourth day and, despite this temporal sequence, changes in BAC were observed. This would suggest that the influence of dosage was probably more closely related to changes in BAC than time. Pieper and Skeen (1973) have shown that the relationship between rate of ehtanol elimination and ethanol dose was statistically significant. However, when the influence of dose was statistically eliminated, time factors were no longer significant. The results of both studies suggest that the critical factor in changes in BAC from repeated exposure appears to be dose dependent, and data from the present study suggests a relationship between shifts in the blood alcohol curve and behavior.

An analysis of alcohol's effects on avoidance responding and EEG patterns in Rhesus monkeys has shown that as the BAC increased from 50–250 mg/100 ml blood, the impairment of passive avoidance was correlated with increased EEG depression (Hogans et al., 1961). Similarly, a negative correlation between peak-to-peak amplitude of individual components of sensory evoked potentials and BAC was found in man (Salamy and Williams, 1973). More recently Kalant et al. (1975) demonstrated that in humans the degree of iampairment on a sensory motor task is independent of the type of alcoholic beverage consumed but highly dependent on the resulting BAC.

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