Psychopharmacology (1981) 73:307–310

Psychopharmacology


*Original Investigations*

# Effects of Alcohol on the Despair Response to Peer Separation in Rhesus Monkeys

Gary W. Kraemer, Daria H. Lin, Elaine C. Moran, and William T. McKinney

Primate Laboratory and Wisconsin Psychiatric Research Institute, University of Wisconsin, 22 N. Charter Street, Madison, Wisconsin 53706, USA

**Abstract.** In humans, alcoholism and depression are often interrelated. This study examines the effects of alcohol on peer separation-induced despair in rhesus monkeys, a proposed nonhuman primate model of depression. Alcohol, at three different dose levels, or placebo was administered to rhesus monkeys undergoing repeated peer separation. Low-dose alcohol (1 g/kg/day) decreased separation-induced despair, whereas high-dose alcohol (3 g/kg/day) exacerbated the despair response as compared to placebo. This biphasic effect of alcohol on the despair response may be analogous to similar effects of alcohol on depression in humans.

**Key words:** Alcohol – Rhesus monkey – Social separation – Despair

Alcohol consumption and addiction are often linked with human depression. It is accepted that a disposition on the part of an individual to consume alcohol, whether for social or physiological reasons, may potentiate depressive episodes (see Mello 1978, for review). However, it is also true that an existent depression may prompt an individual to begin or increase alcohol consumption. There are undoubtedly many factors involved in this interaction. The pharmacological actions of alcohol which alter behavior are poorly understood, and the data from studies on alcohol use in humans strongly suggest that its effects are influenced by factors other than the actual dose of the drug. Examples of variables which appear to be important are family history, prior experience with the drug, expectations of drug effect, and the environment in which the alcohol is consumed (Mello 1978; Omenn 1975; Allman et al. 1972). For these and other reasons, controlled investigation of possible depression-alcohol interrelationships has been difficult.

Nonhuman primates, which have highly developed social behavior and organization, have been used to examine the effects of alcohol on social and physiological variables and, in a separate area, to investigate the possible social and biological basis of depression. It has been observed that monkeys in positions of high social stress, by virtue of their rank in the dominance order, tend to voluntarily consume more alcohol than monkeys in low-stress positions (Cadell and Cressman 1972; Elton et al. 1976). Crowley et al. (1974) found that acute doses of alcohol (2 g/kg) facilitated play, as well as social and nonsocial sexual behavior in group-housed adult male macaques. On the basis of these kinds of data, investigators have suggested that there may be important motivational and behavioral similarities between monkeys and humans with regard to alcohol consumption.

There may also be important similarities between human and nonhuman primate depression (Reite et al. 1974; McKinney 1977). Separation of monkeys from their peer group often results in a depressive episode similar to that observed in humans in contextually similar circumstances, i.e., loss of a affectional object (Akiskal and McKinney 1975; Paykel et al. 1969). The response to experimental separation in rhesus monkeys is characterized by decreased activity (locomotion and environmental exploration) and by postural collapse (huddling) (Kraemer and McKinney 1979; Mineka and Suomi 1978). Furthermore, it has been shown that the severity of the despair response is ameliorated by treatment with imipramine (Suomi et al. 1978), and augmented by catecholamine-depleting agents (Kraemer and McKinney 1979), indicating that there may be pharmacological as well as behavioral parallels between separation-induced despair in monkeys and human depression.

The purpose of the present study was to determine whether alcohol administration could interact with social separation in rhesus monkeys to alter the severity or duration of peer separation-induced despair.

## Materials and Methods

Seven rhesus monkeys (*Macaca mulatta*) (six males and one female, ages 1.5–2.0 years) were used. The monkeys were reared with their mothers from birth to the age of 1–3 months and then separated from their mothers and housed in two peer groups ($N=3$, $N=4$, respectively).

Repeated peer separations of the same group of rhesus monkeys have been found to produce qualitatively similar responses during each separation period (Suomi et al. 1970). This paradigm was used in a repeated-measures design to study the influence of alcohol at different dose levels on the response to separation.

The experiment was conducted over six time blocks (Table 1, part A). Each block consisted of 4 weeks during which the subjects were group housed or separated and treated with placebo or alcohol (Table 1, part B). The monkeys were group housed in a large living cage ($3 \times 0.75 \times 0.75$ m). During the separation phase, they were housed in a single cage which was created by compartmentalizing the group housing cage with Plexiglas panels.

Alcohol was administered at three dose levels (1, 2, and 3 g/kg/day 25% w/v ethanol) in a between-groups crossover design with each group alternately serving as a placebo control. Alcohol solution (8–36 ml) or an equivalent volume/body weight of placebo (tap water) was administered by nasogastric intubation at 12:30 PM 7 days/week to all subjects. To accomplish this, the monkeys were manually restrained for 2–3 min by an experienced monkey handler. The dose levels were selected to have large, moderate, or minimal acute effects on behavior on the basis of

*Offprint requests to:* G. W. Kraemer

0033-3158/81/0073/0307/$01.00

**Table 1.** Alcohol administration and repeated social separation protocol

| Group | Block 1 | Block 2 | Block 3 | Block 4 | Block 5 | Block 6 |
|---|---|---|---|---|---|---|
| *A. Drugging protocol (25% w/v ethanol)* | | | | | | |
| 1 | Alcohol (2 g/kg) | Placebo | Alcohol (1 g/kg) | Placebo | Alcohol (3 g/kg) | Placebo |
| 2 | Placebo | Alcohol (2 g/kg) | Placebo | Alcohol (1 g/kg) | Placebo | Alcohol (3 g/kg) |
| *B. Protocol, basic block* | | | | | | |
| Week | 1 | | 2 | 3 | 4 | |
| Caging | Group | | Separate | Group | Group | |
| Behavior | Social | | Separation | Reunion | Clearout period | |
| Treatment | Alcohol or placebo | | Alcohol or placebo | Alcohol or placebo | Placebo | |

previous reports (Ellis and Pick 1972) and on pilot studies in our laboratory. Throughout the experiment the monkeys received isoniazid-free Purina Monkey Chow and tap water ad libitum. Blood samples were obtained 2.5 h after intubation at the end of each separation week and assayed for ethanol concentration at the Wisconsin State Laboratory of Hygiene, Department of Toxicology.

The monkeys were behaviorally tested 5 days/week at 9 AM and 2 PM. The afternoon testing time was selected because alcohol has its maximum behavioral effect 1.5 h postingestion. The morning time was selected to provide an assessment of behavior before alcohol administration. During a test session each monkey was observed for 5 min and the frequency and duration of 16 operationally defined behaviors were recorded on an automated clock and counter apparatus (Kraemer et al. 1976). The abbreviated definitions for the categories later found to reflect the effects of peer separation or alcohol treatment are as follows: Self-enclosed, fetal-like position with the head lowered to or past the shoulder level (huddle); maintenance of a stable, stationary position with no simultaneous scoreable behavior (passive); tactile or oral exploration or manipulation of the physical surroundings (environmental explore); ambulation of one or more full steps at any speed (locomotion); maintenance of gross body contact with another monkey (contact cling); oral or manual manipulatory examination of or by another monkey (social explore); and rough-and-tumble activity, i.e. wrestling with or without locomotion and/or mutual or nonmutual chase (play).

The presence of tremor or ataxia in each subject was also recorded. All four observers had been previously shown to reliably score the same behaviors (Pearson product correlation $> 0.90$) and were blind to the alcohol dose and treatment regimen between groups.

The data were analyzed using mixed-design harmonic-means analysis of variance. Significant main effects and interactions were identified using a grand analysis of each behavior with drug or placebo treatment, together or separate housing, days within housing condition, and time of day as repeated-measures factors. Point comparisons of significant ($P < 0.05$) main effects and interactions in the grand analysis were made using the Fisher *lsd* as a post hoc contrast (Winer 1962).

## Results

Analysis of the behavioral data did not reveal any significant effects of alcohol versus placebo administration during the morning test sessions. Therefore, the presentation of results will be confined to data obtained in the afternoon test sessions.

*Blood Alcohol Levels and Motor Effects.* The mean concentration of blood alcohol 2.5 h after administration and the weekly mean frequency of observation of ataxia or tremor are presented in Table 2. Ataxia was not observed at a dose of 1 g/kg/day. At 2 g/kg/day, ataxia was observed in weeks 1 and 2 of administration, but declined to near baseline levels by week 3. At 3 g/kg/day, ataxia was observed throughout the 3-week alcohol administration period. Tremors occurred less often than ataxia, but their frequency of occurrence followed the same pattern.

**Table 2.** Mean frequency of ataxia and tremor per week (± SEM, 5 maximum) over three drug administration weeks and blood ethyl alcohol concentration (± SEM) 2.5 h after nasogastric administration of a 25% w/v solution

| Blood alcohol (mg/*100 ml*) *(week 2)* | | | |
|---|---|---|---|
| 1 g/kg/day | 53.7 ± 8.4 | | |
| 2 g/kg/day | 164.9 ± 12.6 | | |
| 3 g/kg/day | 321.0 ± 7.5 | | |
| Week of administration | 1 | 2 | 3 |
| *Ataxia* | | | |
| 1 g/kg/day | 0 | 0 | 0 |
| 2 g/kg/day | 4.3 ± 0.29 | 3.3 ± 0.64 | 0.42 ± 0.30 |
| 3 g/kg/day | 5.0 ± 0.0 | 4.9 ± 0.14 | 5.0 ± 0.0 |
| *Tremor* | | | |
| 1 g/kg/day | 0 | 0 | 0 |
| 2 g/kg/day | 0.14 ± 0.14 | 0.43 ± 0.20 | 0 |
| 3 g/kg/day | 0.42 ± 0.42 | 1.57 ± 0.42 | 0.71 ± 0.42 |

*Effects of Social Separation on Placebo-Treated Monkeys.* While the subjects were separated and treated with placebo, they had a despair response to peer separation similar to that reported in previous studies (Suomi et al. 1970; Kraemer and McKinney 1979). They spent a substantial proportion of their time huddling or engaging in passive behaviors (Table 3).

*Effects of Alcohol on the Social Behavior of Group-Housed Monkeys.* Table 4 shows data for the three social behaviors that were significantly altered by various doses of alcohol. The baseline behaviors of these monkeys were typified by high levels of contact cling, social explore, and, for this age range, surprisingly low levels of play. Alcohol at a dose of 1 g/kg/day did not alter any social behaviors as compared to placebo. At 2 g/kg/day, contact cling was reduced, social explore was not affected, and play was increased as compared to placebo. At 3 g/kg/day, contact cling and play were not significantly different from placebo levels, while social explore was reduced.

**Table 3.** Mean duration (± SEM) of behaviors during group or separate housing conditions (maximum of 300 s)

| | Huddle | | Locomotion | | Environmental explore | | Passive | |
|---|---|---|---|---|---|---|---|---|
| | Group | Separate | Group | Separate | Group | Separate | Group | Separate |
| Placebo | 11.2 ± 6.8 | 55.3 ± 8.0 | 14.9 ± 1.9 | 20.0 ± 2.6 | 33.3 ± 6.2 | 34.6 ± 5.6 | 32.3 ± 5.5 | 85.6 ± 8.6 |
| Alcohol | | | | | | | | |
| 1 g/kg/day | 20.7 ± 16.6 | 23.4 ± 11.0[a] | 31.4 ± 9.9[a] | 44.9 ± 16.7[a] | 51.7 ± 13.6[a] | 50.1 ± 13.3[a] | 21.0 ± 6.0 | 64.6 ± 15.5[a] |
| 2 g/kg/day | 8.3 ± 3.7 | 123.0 ± 18.7[a] | 81.3 ± 14.0[a] | 32.3 ± 5.7[a] | 34.3 ± 9.1 | 54.3 ± 10.3[a] | 43.9 ± 10.9 | 41.4 ± 11.9[a] |
| 3 g/kg/day | 51.0 ± 8.8[a] | 139.7 ± 30.1[a] | 82.7 ± 16.7[a] | 36.9 ± 15.9 | 6.8 ± 2.6[a] | 6.8 ± 2.5[a] | 32.7 ± 14.4 | 77.7 ± 18.8 |

[a] Drug versus placebo, $P < 0.05$

**Table 4.** Mean duration (± SEM) of social behaviors in the group housing condition (maximum of 300 s)

| | Social behavior | | |
|---|---|---|---|
| | Contact cling | Social explore | Play |
| Placebo | 146.9 ± 18.5 | 24.7 ± 5.7 | 0 |
| Alcohol | | | |
| 1 g/kg/day | 165.4 ± 33.2 | 14.6 ± 5.0 | 0 |
| 2 g/kg/day | 68.4 ± 17.7[a] | 22.2 ± 7.9 | 20.0 ± 6.3[a] |
| 3 g/kg/day | 153.1 ± 24.5 | 8.0 ± 1.2[a] | 0 |

[a] Drug versus placebo, $P < 0.05$

These changes in behavior reflect differences in some aspects of social interaction in group-housed animals at moderate to high doses of alcohol. In particular, at a dose of 2 g/kg/day, more time was spent playing and less time was spent contact clinging than was typical with placebo. At a dose of 3 g/kg/day the subjects were patently inebriated. Four categories (huddle, contact cling, locomotion, and passive) accounted for most of the ongoing behavior in the group-housing condition. The animals were too incapacitated to play or engage in social behaviors besides contact cling. They staggered around the cage, sat alone (passive or huddle), or clung to each other.

*Interactions of Alcohol Treatment with the Despair Response.* The occurrence of a despair response to separation has been characterized by low levels of activity, i.e., locomotion and environmental explore combined as an index of activity, paired with elevated levels of huddle and passive. The lowest dose of alcohol ameliorated the despair response, as evidenced by the fact that the monkeys maintained high levels of activity and had low levels of huddling when separated as compared to their placebo separation values. In contrast, the highest dose of alcohol exacerbated the despair response, as evidenced by the increased huddling and decreased activity shown when the animals were separated as compared to their placebo separation values.

The increased huddling and decreased activity that occurred during separation with the higher doses of alcohol might be interpreted as a sedative effect of the drug. However, locomotion increased at high-dose levels when the animals were group-housed, indicating that the direction of effect on this measure was dependent on the housing condition and not on a more global drug response. This suggests that the interaction of alcohol with social separation is more complex than could be accounted for by simple sedative effects.

## Discussion

Alcohol has a biphasic dose effect on the rhesus monkey response to peer separation. At a low dose it ameliorated, and at a high dose it exacerbated the despair response.

Table 5 summarizes the direction of behavioral effects of alcohol at low and high doses in comparison to other drugs examined in previous studies using this paradigm. Alcohol at a dose of 1 g/kg/day has acute effects similar to those observed during treatment with imipramine (Suomi et al. 1978). At higher doses, alcohol shares some behavioral effects in the peer separation paradigm with catecholamine-depleting drugs such as α-methyl-*p*-tyrosine (AMPT), in that both AMPT and high-dose alcohol increase the relative duration of despair behavior observed during social separation (Kraemer and McKinney 1979). However, these similarities with other drugs are paired with some important differences. First, while AMPT increases the severity of the despair response at low doses, it does this without altering behavior in the group situation. Alcohol can also increase the severity of the despair response, but only at doses which significantly alter social behavior in the prior group-housing condition. Second, in the dose ranges studied, catecholamine-depleting drugs tested in this paradigm, unlike alcohol, have monotonic dose-effect curves, increasing or decreasing the duration of particular behaviors with increasing dose. Third, the behavioral effects of alcohol are limited to periods of 3–6 h after administration whereas the catecholamine metabolism-altering drugs (imipramine or AMPT) have longer and more stable durations of action.

One per day alcohol dosages may not compare with the human pattern of consumption and some of the behavioral effects observed in the present study may be peculiar to the schedule of administration. In particular, we did not observe increased tremor in the morning testing sessions, where it might be expected as a withdrawal symptom following high doses of alcohol. It may be necessary to maintain monkeys on more frequent administration schedules over longer time periods to observe withdrawal-related behaviors.

Until a wider spectrum of drugs have been evaluated behaviorally and biochemically, the reliability with which drug effects in this experimental paradigm in monkeys predict similar effects in humans remains speculative. Nevertheless, there are general similarities in the behavioral response to alcohol between monkeys and humans. In monkeys, doses of alcohol below a certain level reduced some of the depression-like behaviors that occur during social separation. This could be a consumption-reinforcing effect of low-dose alcohol. If this effect occurred in humans, it might be a factor in maintaining consumption in depressed individuals, in in-

**Table 5.** Direction of effect of various drugs on social and separation behavior in rhesus monkeys. Locomotion and environmental explore are considered as activity. All social contact behaviors, such as play, social explore, and contact cling are considered as social interaction. AMPT indicates α-methyl-*p*-tyrosine

| | Group-housed behavior | | Separation behavior | |
|---|---|---|---|---|
| | Social interaction | Activity | Huddling (despair) | Activity |
| Alcohol (1 g/kg/day) | No effect | Increase | Decrease | Increase |
| Alcohol (3 g/kg/day) | Increase | Increase | Increase | Decrease |
| Chronic imipramine (10 mg/kg/day) | No effect | No effect | Decrease | Increase |
| AMPT (< 50 mg/kg/day) | No effect | No effect | Increase | Decrease |
| AMPT (> 50 mg/kg/day) | Decrease | Decrease | Increase | Decrease |

dividuals with a depressive response to previously consumed alcohol, or in individuals undergoing significant social stress. High doses of alcohol in humans might augment depressive behavior resulting from events like social separation, as it does in monkeys.

*Acknowledgements.* This research was supported by research grants from NIMH (MH 21892), NICHD (10570), by the Wisconsin Psychiatric Research Institute, and by a predoctoral fellowship to D. Lin (NIGMS GM07058).

## References

Akiskal HS, McKinney WT (1975) Overview of recent research in depression: Integration of ten conceptual models into a comprehensive clinical frame. Arch Gen Psychiatry 32:285–305

Allman LR, Taylor AH, Nathan PE (1972) Group drinking during stress: Effects on drinking behavior, affect, and psychopathology. Am J Psychiatry 129:669–678

Cadell TE, Cressman R (1972) Group social tension as a determinant of alcohol consumption in *Macaca mulatta*. J Med Primatol 250–259

Crowley TJ, Stynes AJ, Hydinger M, Kaufman IC (1974) Ethanol, methamphetamine, pentobarbital, morphine, and monkey social behavior. Arch Gen Psychiatry 31:829–838

Ellis FW, Pick JR (1972) Ethanol dependence in rhesus monkeys. J Med Primatol 237–240

Elton RH, Greaves DA, Bunger DR, Pyle TW (1976) Drinking patterns of pigtailed macaques. J Stud Alcohol 37:1548–1555

Kraemer GW, McKinney WT, Prange AJ, Breese GR, McMurray TM, Kemnitz J (1976) Isoniazid: Behavioral and biochemical effects in rhesus monkeys. Life Sci 19:49–60

Kraemer GW, McKinney WT (1979) Interactions of pharmacological agents which alter biogenic amine metabolism and depression: An analysis of contributing factors with a primate model of depression. J Affect Disorders 1:33–54

McKinney WT (1977) Animal behavioral biological models relevant to depressive and affective disorders in humans. In: Schulferbrandt JG, Raskin A (eds) Depression in childhood: Diagnosis, treatment and conceptual models. Raven, New York, pp 107–122

Mello NK (1978) Alcoholism and the behavioral pharmacology of alcohol: 1967–1977. In: Lipton MA, DiMascio A, Killam KF (eds) Psychopharmacology: A generation of progress. Raven, New York, pp 1619–1637

Mineka S, Suomi SJ (1978) Social separation in monkeys. Psychol Bull 85:1376–1400

Omenn GS (1975) Alcoholism: A pharmacogenetic disorder. Mod Probl Pharmacopsychiatry 10:12–22

Paykel ES, Myers JK, Dienelt MN, Klerman GL, Lindenthal JJ, Pepper MP (1969) Life events and depression. Arch Gen Psychiatry 21:753–760

Reite M, Kaufman IC, Pauley JD, Stynes AJ (1974) Depression in infant monkeys: Physiological correlates. Psychosom Med 36:363–367

Suomi SJ, Harlow HF, Domek CJ (1970) Effect of repetitive infant-infant separation of young monkeys. J Abnorm Psychol 76:161–172

Suomi SJ, Seaman SF, Lewis JK, DeLizio RD, McKinney WT (1978) Effects of imipramine treatment of separation-induced social disorders in rhesus monkeys. Arch Gen Psychiatry 35:321–325

Winer BJ (1962) Statistical principles in experimental design. McGraw Hill, New York

Received September 8, 1980; Final version December 19, 1980