Drug and Alcohol Dependence, 19 (1987) 17—27
Elsevier Scientific Publishers Ireland Ltd.

THE EFFECTS OF FOOD DEPRIVATION ON THE SELF-ADMINISTRATION OF PSYCHOACTIVE DRUGS

RENÉ DE LA GARZA* and CHRIS E. JOHANSON**

Department of Psychiatry, The University of Chicago, Pritzker School of Medicine, Drug Abuse Research Center, 5841 S. Maryland Ave., Chicago, IL 60637 (U.S.A.)

(Received September 19th, 1986)

SUMMARY

Under conditions of food deprivation, relative to the equivalent satiation condition, increases in the self-administration of *d*-amphetamine in three out of three monkeys, of cocaine in two out of three monkeys, and of nicotine in one out of three monkeys, were observed. Furthermore, these increases were dose-dependent, i.e. with low doses there were large increases in number of infusions, but with high doses there were no differences in number of infusions between the two feeding conditions. For some doses of diazepam there were increases in number of infusions under the deprivation condition relative to the satiation condition, but these increases were not statistically significant. In contrast, food deprivation produced slight, but significant, increases in the number of perphenazine infusions in one monkey but inappropriate level responses were also high for this monkey as well. In most cases, increases under food deprivation occurred with drugs that already maintained responding above saline under satiation conditions. Therefore, food deprivation does not appear to convert non-reinforcers into reinforcers, but instead increases intake of drugs that function as reinforcers. This effect may contribute to the persistence of psychomotor stimulant drug-seeking behavior in humans.

Key words: Satiation — Deprivation — Self-administration — Cocaine — *d*-Amphetamine — Nicotine — Diazepam — Perphenazine

INTRODUCTION

Food deprivation enhances the rate of self-administration of commonly abused substances. In experimental animals, drugs such as cocaine [1—3],

*Present address: University of Colorado, Health Sciences Center, Department of Pharmacology C236, 4200 East Ninth Avenue, Denver, CO 80262, U.S.A.
**To whom requests for reprints should be sent.

0376-8716/87/$03.50

d-amphetamine [4,5], ethanol [6,7], nicotine [8], phencyclidine [1,9], and pentobarbital [10] maintain higher rates of responding under conditions of food deprivation than under satiation. Additionally, some studies have found interactions between drug dose and food deprivation. For example, it has been shown that the rate-increasing effects of food deprivation are dose-dependent for *d*-amphetamine, phencyclidine, and pentobarbital; that is, large increases in total number of infusions are obtained when relatively low doses of these drugs are tested, but few changes occur in the total number of infusions with higher doses [11].

Despite the dramatic changes in drug self-administration produced by food deprivation, its effects have not been thoroughly evaluated using psychoactive drugs with marginal reinforcing value. Some studies, however, suggest that food deprivation has different effects when these substances are investigated. For example, Takahashi and Singer [12] studied the active ingredient of cannabis (Δ^9-THC) under a schedule induction procedure [13] and found both acquisition and maintenance of intravenous self-administration under deprivation conditions, but only in combination with a concurrent fixed time (FT) 1-min schedule of food delivery. In the absence of the FT schedule, food-deprived rats did not self-administer Δ^9-THC. In contrast, food sated rats did not self-administer Δ^9-THC in the presence or absence of the FT schedule of food delivery. Similar findings have been reported for methadone [14] using the same procedures. Although studies have shown that intravenous cocaine and phencyclidine are readily self-administered [1,2], these drugs do not maintain *oral* self-administration in sated rats and furthermore food deprivation does not enhance their self-administration by this route [11]. These studies, therefore, suggest that food deprivation may increase the rate of self-administration of drugs that already maintain responding, but this condition alone may not be sufficient to generate self-administration of substances that do not maintain operant behavior under food satiation conditions.

The present experiment investigated whether drugs that have marginal or no reinforcing value under fixed-ratio schedules, including nicotine, diazepam and perphenazine, can function as reinforcers under deprivation conditions. Cocaine and *d*-amphetamine were also tested as standards of comparison to other studies. This experiment also investigated the combined effects of dose and feeding condition by conducting complete dose-effect determinations. Finally, this study investigated the effects of feeding conditions on intravenous drug self-administration in primates in an attempt to extend findings obtained in rats to a different species.

METHODS

Subjects

Three male rhesus monkeys (0038, 1027, 1032) were used in this study. The monkeys weighed 7.3 (0038), 7.2 (1027), and 11.4 kg (1032) at the

beginning of the study. One of the monkeys (0038) had participated previously in a self-administration study with responding maintained by cocaine and procaine [15]. The other two monkeys were experimentally naive at the beginning of the study. Monkeys had continuous access to water and were given supplemental vitamins several days each week.

Each monkey was surgically prepared with a single lumen silicone catheter (Rodhelm Reiss, Co., Belle Mead, NJ). The surgical procedure was performed under sodium pentobarbital anesthesia (up to 30 mg/kg, i.v) under aseptic conditions. One end of the catheter was inserted into a major vein (internal and external jugulars, femorals) and threaded for a distance calculated to terminate in or near the right atrium of the heart. The distal end was threaded subcutaneously to the back of the animal, exiting the skin through a small incision between the scapulae. The subjects were treated with a broad spectrum antibiotic (Keflin, Lilly Co., Indianapolis, IN) when there was evidence of a catheter tract infection. When a catheter became dislodged, the monkey was removed from the experiment for several days. Subsequently, a replacement catheter was surgically implanted into one of the remaining veins and the monkey was returned to the experiment 1 or 2 days later.

Apparatus

Each monkey was housed in a sound attenuating wooden cubicle (inside dimensions: 70 × 80 × 70 cm) that served as the experimental space. Each cubicle was equipped with a fan for ventilation and masking of extraneous sounds. A convex lens inserted into the front door allowed visual inspection of the monkey. Two metal boxes (12.5 × 15 × 10 cm) were mounted on the inside of the front door of the cubicle about 23 cm from each other. Each box contained a response lever (PRL-001, BRS/LVE, Beltsville, MD) and four stimulus lights. Two of these lights were covered with red lens caps and two were covered with white lens caps. The cubicle could be illuminated by either a red or white overhead light.

Each monkey wore a stainless steel harness connected to a spring arm 42—47 cm long (E & H Engineering, Chicago, IL). The spring arm was attached to the back of the cubicle allowing the monkey relatively unrestricted movement within the cubicle and provided protection for the catheter which was threaded through the arm. Outside the cubicle the catheter was connected to a peristaltic infusion pump (7540×, Cole-Parmer Instrument Co., Chicago, IL) which delivered solutions at the rate of 6 ml/min. Cables connected the experimental cubicle to solid state programming and recording equipment located in an adjacent room.

Procedure

For the two naive monkeys (1027, 1032), lever pressing was shaped by baiting the lever with food. The number of responses required to obtain an infusion of cocaine (0.1 mg/kg) was gradually increased within the

course of the first five sessions. The other monkey (0038) was placed on the terminal conditions from the beginning of this study. Throughout the study, responding on the right lever was maintained under a fixed-ratio 10 schedule of drug delivery (10 responses/drug infusion, FR 10) in the presence of the white overhead and lever lights during 3-h daily sessions. During drug delivery, the white lights were extinguished and the red overhead and lever lights were illuminated for the duration of the 10-s infusion. For all monkeys, responding on the left lever had no programmed consequences. The training dose of cocaine (0.1 mg/kg) was used as the baseline drug throughout the study.

After responding stabilized (the number of infusions within ±10% of their mean for at least three consecutive sessions), several doses of diazepam (0.025—4.0 mg/kg), *d*-amphetamine (0.002—0.06 mg/kg), nicotine (0.008—0.25 mg/kg), perphenazine (0.001—0.1 mg/kg), and cocaine (0.008—0.25 mg/kg) were substituted for the baseline dose of cocaine under both free-feeding (satiation) and food-restricted (deprivation) conditions. For monkeys 1027 and 1032, all of the dose-response functions were initially determined under the satiation condition and repeated subsequently under the deprivation condition. For monkey 0038, satiation and deprivation conditions were alternated twice followed by an additional satiation condition but not all drugs were tested during each cycle. For monkey 0038, except for cocaine and diazepam, the dose-response function was determined first under a satiation feeding condition and then redetermined under deprivation. Cocaine and diazepam were tested in the opposite order. Under each feeding condition, drugs were tested in a mixed order across monkeys. During the transitions between feeding conditions, daily sessions with the baseline drug were conducted.

Each drug dose was substituted until one of the two conditions were met: (1) three successive sessions of stable responding (the number of infusions within ±10% of their mean) were obtained, or (2) the data showed no upward or downward trends in responding over the entire substitution period. The animals were returned to the cocaine baseline condition between successive dose substitutions. The dose-response function for cocaine, however, was obtained without returning to the baseline cocaine dose after other cocaine doses were tested. The appropriate vehicle for each drug was tested after the determination of each dose-response function until responding declined to low levels for 3 consecutive sessions.

Under deprivation conditions, the monkeys were reduced to 75—85% of free-feeding weights by restricting their daily ration of Purina monkey chow, given immediately after the 3-h session was completed. The monkeys were weighed at least once every 2 weeks and drug concentrations adjusted. Phencyclidine (1.0 mg/kg) was given at the time of weighing to facilitate handling.

Data analyses

The total number of infusions during the last three sessions of each

test dose was used for the analysis of the effects of the two feeding conditions. A drug dose was considered to be a positive reinforcer if the range in number of infusions around the mean did not overlap with the range in number of control vehicle infusions. In order to determine whether the deprivation condition enhanced the rate of self-administration relative to the satiation condition, the number of infusions for drug doses tested under the two feeding conditions were statistically compared with a repeated-measures ANOVA [16].

Drugs

Cocaine hydrochloride and *d*-amphetamine sulfate were supplied by the National Institute on Drug Abuse. Diazepam base was a gift of Hoffman-La Roche, Inc. (Nutley, NJ). Nicotine bitartrate and injectable perphenazine were obtained commercially. The drug salts were dissolved in physiological saline and the doses were calculated from the salt. Injectable perphenazine was also dissolved in physiological saline, but doses were calculated from the base. Diazepam base was first dissolved in a stock containing 50% ethyl alcohol and 50% emulphor 620 and subsequently diluted in saline to the desired concentrations. The diazepam doses were calculated from the base.

RESULTS

The baseline dose of cocaine (0.1 mg/kg) maintained responding above saline under both feeding conditions in all monkeys. Regardless of the feeding condition, drug substitutions required between 3 and 12 sessions and no reliable relation was observed between dose and the number of sessions required to reach stability (data not shown).

Figure 1 shows the results obtained with *d*-amphetamine and cocaine and Fig. 2 shows the results obtained with nicotine under the two feeding conditions. *d*-Amphetamine, cocaine and nicotine maintained self-administration above saline levels under both feeding conditions and, in general, the number of infusions self-administered was greater under food deprivation conditions. However, there were differences in effect both across drugs and monkeys. *d*-Amphetamine maintained higher levels of self-administration under the deprivation condition than under the satiation condition in all monkeys. A repeated-measures ANOVA analysis of the 2 *d*-amphetamine dose-response functions for monkeys 0038, 1027 and 1032 showed significant differences between the feeding conditions [monkey 0038 $F(1,4) = 46.214, P < 0.01$; monkey 1027 $F(1,4) = 36.069$, $P < 0.01$; monkey 1032 $F(1,4) = 55.209, P < 0.01$]. For all monkeys, the dose of *d*-amphetamine and the deprivation condition interacted, i.e. the number of infusions maintained by the low doses was increased over the number obtained in the equivalent satiation condition, but high doses did not show differences between conditions. Interestingly, for monkey 1027, at doses where responding on the appropriate lever was relatively high, responding on the inappropriate lever was also elevated (Table I).

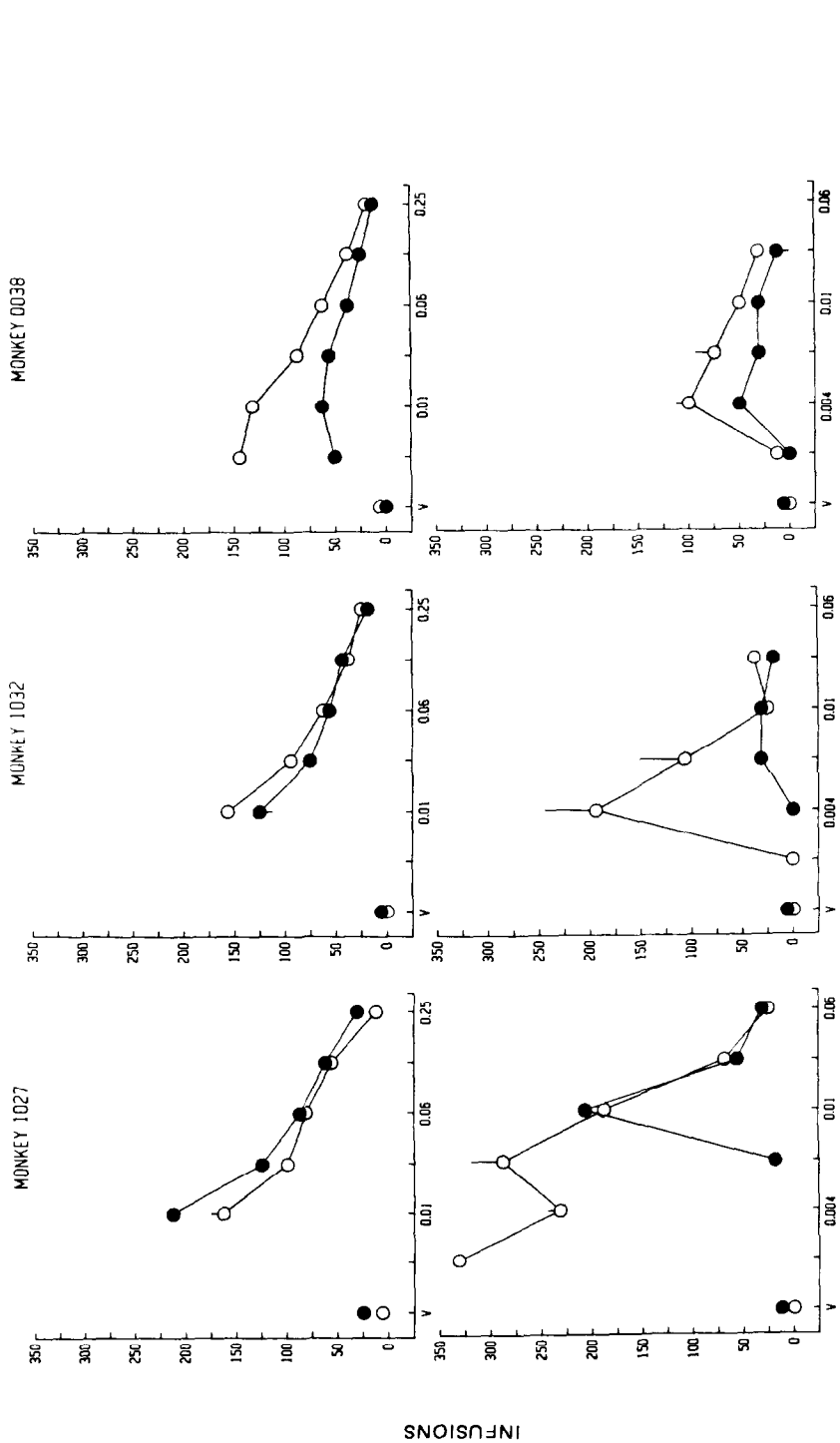

Fig. 1. Total number of infusions for cocaine (top panels) and *d*-amphetamine (bottom panels) obtained during the 3-h session averaged over the last three substitution sessions for each dose tested for individual monkeys. Both the deprivation (opened symbols) and satiation (closed symbols) conditions are included in each panel.

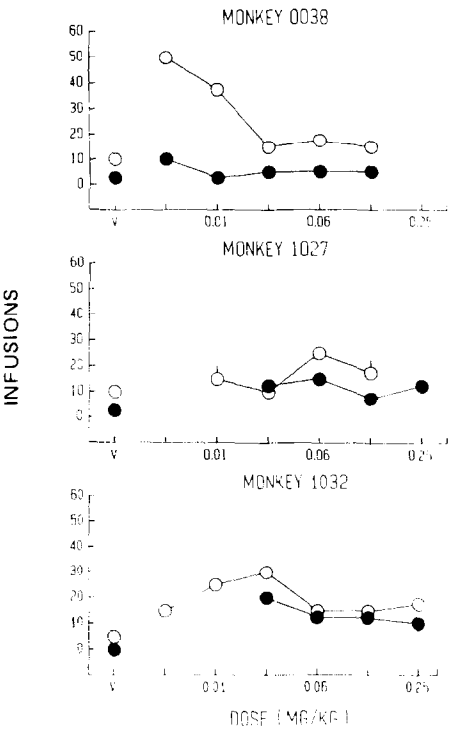

Fig. 2. Total number of infusions for nicotine obtained during the 3-h session averaged over the last three substitution sessions for each dose tested for individual monkeys. Both the deprivation (opened symbols) and satiation (closed symbols) conditions are included in each panel.

For monkeys 0038 and 1032, cocaine maintained higher levels of self-administration under the deprivation condition than under the satiation condition. Monkey 1027, in contrast, maintained higher levels of cocaine self-administration under the satiation condition than under the deprivation condition. A repeated-measures ANOVA revealed that the cocaine dose-response functions for monkeys 0038 and 1032 were significantly different across feeding conditions [$F(1,4) = 214.551, P < 0.01$ for monkey 0038 and $F(1,4) = 10.09, P < 0.05$ for monkey 1032]. The cocaine dose-response functions for monkey 1027 were also significantly different [$F(1,4) = 15.19, P < 0.05$], although in the opposite direction. For monkeys 0038 and 1032, a dose-dependent interaction was found under the deprivation condition, i.e. with low doses, the number of infusions increased relative to the equivalent satiation condition, but with high doses there were no differences.

Although nicotine maintained self-administration under both feeding conditions in all monkeys, the total number of infusions was small compared to the levels maintained by cocaine and *d*-amphetamine (Fig. 2). Under

TABLE I

NUMBER OF INCORRECT LEVER RESPONSES EMITTED BY MONKEY 1027 DURING DRUG SUBSTITUTION SESSIONS

Mean number of incorrect lever responses that monkey 1027 emitted during each drug substitution condition averaged over the last three sessions of each substitution.

	Satiation	Deprivation
Cocaine		
SAL	204.3	115.3
0.01	1949.5	1905.3
0.03	1122.0	1233.7
0.06	8063.0	939.3
0.10	550.7	645.0
0.25	292.0	167.3
d-Amphetamine		
SAL	166.8	56.0
0.002	—	3467.3
0.004	—	2541.3
0.008	149.3	2334.0
0.010	1919.7	2212.7
0.030	2409.7	809.3
0.060	304.7	293.7
Nicotine		
SAL	45.3	115.3
0.01	—	140.3
0.03	122.7	97.3
0.06	124.7	268.3
0.12	75.0	102.3
0.25	119.0	—
Perphenazine		
SAL	119.0	56.0
0.001	193.0	409.3
0.010	92.7	390.7
0.100	63.7	—

the food deprivation condition nicotine intake was increased relative to the equivalent satiation condition, but a repeated-measures ANOVA revealed that only the nicotine dose-response curves for monkey 0038 were significantly different [$F(1,4) = 186.964, P < 0.01$]. The increases observed in monkey 0038 under the deprivation condition were also inversely related to dose.

Figure 3 shows the dose-response curves for diazepam and perphenazine under the two feeding conditions. In monkey 0038, diazepam maintained self-administration above saline levels under both the deprivation (0.1

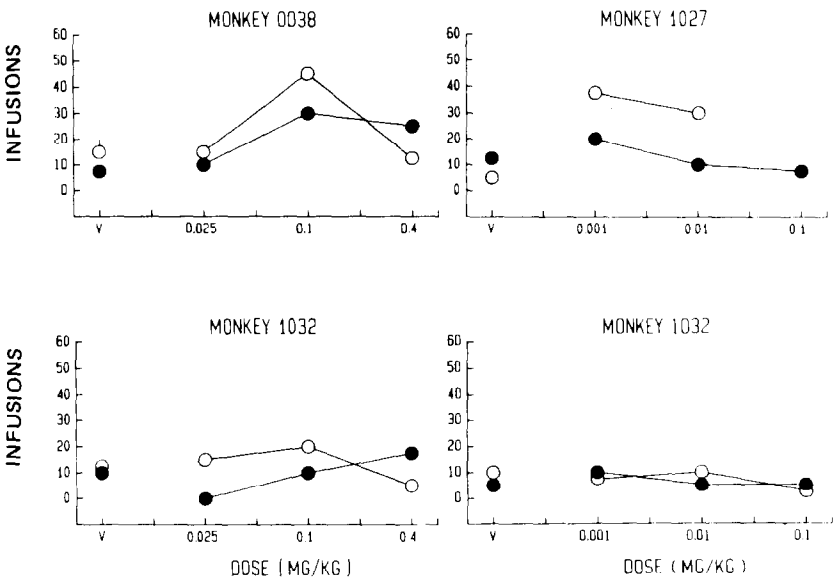

Fig. 3. Total number of infusions for diazepam (left panels) and perphenazine (right panels) obtained during the 3-h session averaged over the last three substitution sessions for each dose tested for individual monkeys. Both the deprivation (opened symbols) and satiation (closed symbols) conditions are included in each panel.

mg/kg and satiation (0.1 and 0.4 mg/kg) conditions. A repeated-measures ANOVA revealed that differences between the two functions were not significant [$F(1,4) = 1.528, P > 0.05$]. For monkey 1032, neither diazepam or perphenazine produced self-administration above vehicle levels and the repeated-measures ANOVA failed to show significant differences between the dose-response curves [$F(1,4) = 0.703, P > 0.05$ for diazepam and $F(1,4) = 0.497, P < 0.05$ for perphenazine]. In monkey 1027 perphenazine did not maintain self-administration above vehicle levels under the food satiation condition, but perphenazine served as a reinforcer under the deprivation condition and a repeated-measures ANOVA of the dose-response curves showed a significant difference [$F(1,4) = 27.64, P < 0.01$]. Monkey 1027, however, responded frequently on the inappropriate lever when this drug was tested (see Table 1).

DISCUSSION

Food deprivation increased the level of self-administration of *d*-amphetamine, cocaine and nicotine compared to the levels maintained under satiation conditions. In the case of nicotine, however, the effects of food deprivation were small and significant only for monkey 0038. Similarly, food deprivation failed to increase perphenazine and diazepam self-admini-

stration in a consistent manner across monkeys. Therefore, food deprivation did not 'convert' a non-reinforcer into a reinforcer. With the exception of monkey 1027 under perphenazine, food deprivation, at best, increased the reinforcing effects of drug doses that already functioned as reinforcing events under satiation conditions.

In some monkeys, low doses of *d*-amphetamine and nicotine failed to maintain self-administration under satiation conditions. However, these doses maintained self-administration under deprivation conditions and these changes can best be described as shifts to the left in the dose-response function for reinforcement rather than the generation of a reinforcer from a nonreinforcer. These data, together with previous findings with Δ^9-THC and methadone [12,13] and oral cocaine and phencyclidine [11], suggest that the effects of food deprivation are limited to drugs that already function as reinforcers under other conditions.

Monkey 1027 responded on the inactive lever under all food access and drug conditions. Even with *d*-amphetamine, the drug that showed the largest difference between food access conditions, many inappropriate lever responses occurred. Therefore, it is possible that a general increase in activity may account, in part, for the occurrence of drug lever responses in this monkey. However, since this cannot account for changes observed in other monkeys, this possibility is unlikely.

Under the food deprivation condition relative to the results under the equivalent satiation condition, *d*-amphetamine produced the largest increases in total number of infusions than any of the other drugs tested and this effect was consistent across monkeys. *d*-Amphetamine also interacted with food deprivation in a dose-dependent manner since low doses produced large increases in self-administration, but high doses did not differ from the equivalent satiation condition. These findings replicate previous observations [4] using orally administered *d*-amphetamine and extend their findings to the intravenous route. Food deprivation effects on *d*-amphetamine self-administration are comparable to the effects produced on pentobarbital self-administration [10,17]. The similarity of these effects are important because these drugs produce opposite effects on food intake in monkeys, i.e. *d*-amphetamine decreases and pentobarbital increases food intake [18, 19]. Hence, the effects of food deprivation on drug-seeking behavior are not dependent on the effects of these compounds on food intake, but rather these effects represent a more complex interaction not yet fully understood [11].

In summary, food deprivation enhances the reinforcing value of a drug dose if the drug already functions as a reinforcing event under conditions of satiation. That is, food deprivation does not appear to 'convert' a non-reinforcer into a reinforcer. There are various behavioral techniques that may be utilized to generate a reinforcer from a previously neutral event, e.g. chaining and second-order contingencies, but the feeding condition by itself does not appear to increase the likelihood of drug-seeking behavior of a drug that is not reinforcing under satiation conditions.

The effects of food deprivation on drugs with dependence potential are experimentally reproducible in several species and sometimes dramatic in size. The extent to which this variable interacts with human drug-seeking behavior is poorly understood and seldom studied. Because of the large changes produced by food deprivation this variable may be a contributing factor in the persistence of human drug-seeking behavior.

ACKNOWLEDGMENT

This research was funded by a research grant from the National Institute on Drug Abuse, DA00250.

REFERENCES

1 M.E. Carroll, C.P. France and R.A. Meisch, J. Pharmacol. Exp. Ther., 217 (1981) 241.
2 R. de la Garza, J. Bergman and C.R. Hartel, Pharmacol. Biochem. Behav., 15 (1981) 141.
3 M. Papasava, T.P.S. Oei and G. Singer, Pharmacol. Biochem. Behav., 15 (1981) 485.
4 M.E. Carroll and D.C. Stotz, J. Pharmacol. Exp. Ther., 227 (1983) 28.
5 R.N. Takahashi, G. Singer and T.P.S. Oei, Pharmacol. Biochem. Behav., 9 (1978) 857.
6 R.A. Meisch and T. Thompson, Psychopharmacologia, 22 (1971) 72.
7 T.A. Roehrs and H.H. Samson, Pharmacol. Biochem. Behav., 16 (1982) 393.
8 W.J. Lang et al., Pharmacol. Biochem. Behav., 7 (1977) 65.
9 M.E. Carroll and D.C. Stotz, Psychopharmacology, 84 (1984) 299.
10 D.J. Kliner and R.A. Meisch, Pharmacol. Biochem. Behav., 16 (1982) 579.
11 M.E. Carroll and R.A. Meisch, in: T. Thompson, P.B. Dews and J.E. Barret (Eds.), Advances in Behavioral Pharmacology, Vol. 4, New York, Academic Press, 1984, pp. 47—88.
12 R.N. Takahashi and G. Singer, Pharmacol. Biochem. Behav., 13 (1980) 877.
13 J.L. Falk, Physio. Behav., 4 (1969) 421.
14 T.P.S. Oei et al., in: F. Colpaert and J. Rosecrans (Eds.), Amsterdam, Elsevier/North-Holland Biomedical Press, 1978, pp. 503—516.
15 R. de la Garza and C.E. Johanson, Pharmacol. Biochem. Behav., 17 (1982) 1295.
16 W.L. Hays, Statistics (3rd edn), New York, Holt, Rinehart and Winston, 1981.
17 R.A. Meisch, Paper presented at the 90th APA Convention, Washington D.C., (1982).
18 R.W. Foltin and C.R. Schuster, J. Pharmacol. Exp. Ther., 226 (1983) 405.
19 R.W. Foltin, S. Ellis and C.R. Schuster, Pharmacol. Biochem. Behav., 23 (1985) 249.