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ORIGINAL INVESTIGATION

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Food deprivation affects extinction and reinstatement of responding in rats

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Abstract Food deprivation has been shown to increase the self-administration of a wide variety of drugs in a number of different species. However, the effects of food deprivation on other phases of drug taking have not been established. The purpose of the present study was to evaluate the effects of food deprivation on reinstatement of responding for cocaine. Rats trained to self-administer 0.2, 0.4, or 1.0 mg/kg cocaine intravenously (IV) under a fixed-ratio 1 schedule for the first 2 h during daily 7-h sessions were fed either before or after the experimental session. During hours 3–7, rats self-administered saline. Saline replaced cocaine in the infusion pumps at the beginning of hour 3 and a priming injection of either saline or cocaine (0.32, 1.0, or 3.2 mg/kg IV) was administered at the beginning of hour 4. The number of infusions that was self-administered was measured throughout the 7-h session. During hours 1 and 2 when cocaine was available, the number of infusions was inversely related to cocaine dose. During hour 3, rats typically self-administered several infusions of saline, which gradually decreased to near-zero levels by hours 4–7 (extinction responding). A priming injection of cocaine administered at the beginning of hour 4 reinstated responding in a dose-related manner. The magnitude of extinction responding during hour 3 and reinstatement of responding during hour 4 were similar regardless of cocaine maintenance dose. However, responding during hour 4 did increase in all cocaine maintenance dose groups when rats were fed before versus after the session. The effects of food deprivation level (8–12 g, 20 g, unlimited food) and time of feeding (before versus after the session) were also assessed in rats maintained at 0.4 mg/kg cocaine. While the magnitude of reinstatement of responding during hour 4 did not vary as a function of food level, extinction responding during hour 3 was significantly increased in rats maintained at the lowest food level (8–12 g) when feeding occurred after the session. These results suggest that food deprivation level and time of feeding, but not cocaine maintenance dose, are important variables in altering extinction and reinstatement of responding.

Key words Cocaine · Extinction · Food deprivation · Intravenous · Maintenance dose · Rats · Reinstatement of responding · Relapse · Self-administration

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Introduction

Several studies have shown that food deprivation has an important influence on drug self-administration in laboratory animals (Carroll and Meisch 1979, 1984; Carroll et al. 1981; de la Garza and Johanson 1987; Files et al. 1993). A high rate of comorbidity between eating disorders, such as anorexia and bulimia, and drug abuse in humans has also been noted by several investigators (Jonas and Gold 1987; Jonas et al. 1987; Zweben 1987; McElroy and Mirin 1992). Approximately one-third of callers to the National Cocaine Hotline who met DSM-III criteria for cocaine abuse also met DSM-III criteria for bulimia and/or anorexia nervosa, a rate more than double that of the normal population (Jonas et al. 1987). Although comorbidity does not imply causality, the relationship between eating disorders and drug abuse is interesting to note. Furthermore, early studies showed that humans increased coffee consumption and intake of tobacco products (Franklin et al. 1948), as well as coca-leaf chewing (Hanna and Hornick 1977), when they were maintained under restricted diets. Studies by Hall and coworkers (1986) and Niaura (1992) also showed that cigarette consumption increased as a result of food restriction, and Bulik and Brinded (1994) showed that the total amount of time spent working for cigarettes increased after a period of food deprivation.

More extensive research on the effects of food deprivation on drug self-administration has been conducted in laboratory animals. Several variables including schedule

of reinforcement, dose of drug that is self-administered, and route of drug administration influence the degree to which self-administration is altered by food deprivation (for review, see Carroll and Meisch 1984). The magnitude of the food deprivation effect also depends on body weight, daily food allotment, and method of food deprivation. In general, self-administration of drugs that readily serve as reinforcers (e.g., cocaine, opiates, and PCP) increases under food deprivation conditions, while self-administration is not altered by food deprivation when the maintenance drug (e.g., diazepam) is not readily self-administered (Carroll et al. 1981; de la Garza and Johanson 1987). The generality of the food-deprivation effect is denoted by the fact that the self-administration of drugs from a wide range of pharmacological classes, in a number of different species, under several different schedules of reinforcement increases under food-deprivation conditions (Carroll and Meisch 1984). In addition to the maintenance phase of drug self-administration, food deprivation also affects the acquisition (Carroll et al. 1989; DeVry et al. 1989; Carroll and Lac 1993) and withdrawal (Carroll and Carmona 1991) phases of drug taking.

Of particular importance to the current study is another important phase in the drug addiction process: relapse to drug use. Several studies have shown that environmental stimuli associated with drug self-administration can profoundly influence drug-seeking behaviors (Wikler and Pescor 1967; Goldberg et al. 1969, 1979; Goldberg 1970, 1973). In one model used in both rats and monkeys, drug self-administration is extinguished by replacing drug with saline (Stretch and Gerber 1973; Davis and Smith 1974, 1976; Gerber and Stretch 1975; de Wit and Stewart 1981, 1983; Comer et al. 1993). In this model, the presentation of exteroceptive stimuli, such as lights or tones, previously associated with drug reinstates responding during the extinction period (e.g., Davis and Smith 1974, 1976). An analogous situation has been noted in abstaining human drug abusers who often relapse following exposure to drug-abusing peers, drug paraphernalia, or locations where previous drug use occurred (O'Brien 1976; Gawin 1991).

In addition to the presentation of external stimuli during the extinction period, the effects of interoceptive stimuli on reinstatement of responding was also examined. For example, Carroll (1985) showed that when rats were food-deprived during the extinction period, reinstatement of responding occurred. It was concluded that the interoceptive stimuli produced by food deprivation became associated with the reinforcing effects of cocaine, resulting in a reinstatement of drug-taking behaviors (i.e., lever-pressing). Non-contingent, experimenter-administered (priming) injections of drug also produce interoceptive stimuli that result in a reinstatement of responding. The magnitude of the reinstatement of responding that occurs following priming injections of drug during the extinction period varies depending on the dose, as well as the pharmacological class of the priming drug (Gerber and Stretch 1975; de Wit and Stewart 1981, 1983; Slikker et al. 1984; Comer et al. 1993; Worley et al. 1994). To date, however, no studies of relapse have investigated how the maintenance dose of the reinforcer or how different levels of food deprivation may alter reinstatement of responding produced by priming injections of drug. The purposes of the present study were to evaluate the effects of priming injections of cocaine (0.32, 1.0 and 3.2 mg/kg IV) administered during an extinction period in rats trained to self-administer 0.2, 0.4 or 1.0 mg/kg per injection cocaine when they were maintained under three different feeding conditions (8–12 g food, 20 g food, and food satiation). The variables were also compared under conditions where the rats were fed before or after the daily 7-h session to examine the difference between acute and chronic food deprivation/satiation.

Materials and methods

Subjects

Experimentally naive, male Wistar rats (Harlan Sprague-Dawley, Madison, Wisc.) were initially housed in individual stainless-steel cages in a temperature-controlled room (24°C; lights on at 6:00 a.m., off at 6:00 p.m.) for at least 3 days following arrival in the laboratory. Food and water were freely available during this acclimation period. Rats weighed an average of 408.3 (±7.9) g at the beginning of the experiment. Following the acclimation period, each rat was surgically implanted with a chronic indwelling cannula into the left jugular vein, as originally described by Weeks (1972) and modified by Carroll et al. (1981), and placed in individual operant chambers where they were housed for the duration of the experiment. The experimental protocol was approved by the University of Minnesota Institutional Animal Care and Use Committee under protocol number 8910037.

Apparatus

Octagonally shaped experimental chambers consisting of alternating walls of Plexiglas and stainless-steel (see Carroll et al. 1981 for a detailed description of the chambers) were used. Each experimental chamber was enclosed in a sound-attenuating box containing a ventilation fan. Two response levers (Coulbourn Instruments, Lehigh Valley, Pa.), a tongue-operated, solenoid-driven drinking device, and a food receptacle, were located on separate stainless-steel walls of the chamber. Three colored stimulus lights (4.76 W) were located 5 cm above the response levers. A white light (4.76 W) located above the drinking device indicating water availability and a white house light (4.76 W) located above the right response lever were constantly illuminated, except for a 30-min time-out period immediately prior to the start of the experimental session during which time all lights were turned off and responding had no programmed consequences. During the time-out period, data from the previous day were collected, food and water intake from the previous day was measured, and a cocaine pump replaced the saline pump. The start of the experimental session was signaled by the illumination of the house light and the drinking light. Responding on one lever (the "active" lever) activated the infusion pump and the stimulus lights above that lever. Responding on the other lever (the "inactive" lever) activated the stimulus lights above that lever but not the infusion pump and was used to measure nonspecific changes in activity. Infusion pumps (Fluid Metering, RHSYOCKC, Oyster Bay, N.Y.) delivered either drug or saline through Tygon tubing (Fisher Scientific, Springfield, N.J.; inner diameter 0.51 mm, outer diameter 1.52 mm) to a swivel (Alice King Chatham, 050–0022, Hawthorne, Calif.). The swivel

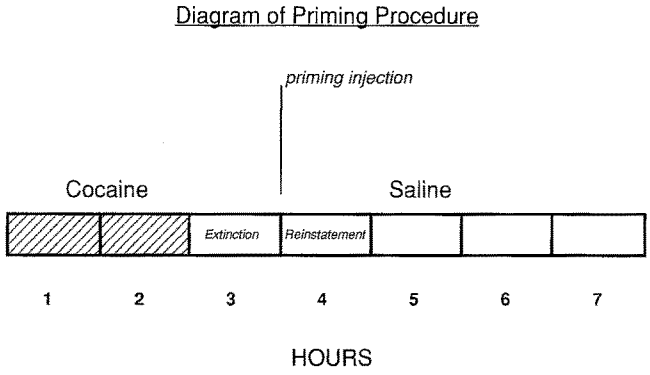

Fig. 1 Diagram of the priming procedure and session events

was in turn connected to a spring-covered plastic cannula (Plastics One, Roanoke, Va.) that was attached to the rat by cannula guides anchored to the skin near the scapulae. Microcomputer Control Systems (Micro Interfaces, Minneapolis, Minn.) computers were used for programming and data collection.

Drugs

Cocaine HCl, obtained from the National Institute on Drug Abuse (Research Triangle Institute, Research Triangle Park, N.C.), was dissolved in sterile saline. Cocaine and saline were stored outside the experimental chambers in 500-ml aspirator bottles covered with surgical mask material to prevent dust and other debris from contaminating the solutions. Either cocaine or saline was delivered by the infusion pump at a rate of 0.03 ml/s. Infusion duration was 1 s/100 g body weight (i.e., between 4 and 4.5 s), resulting in a volume of approximately 0.125 ml per infusion. Maintenance dose was manipulated by changing the concentration of cocaine in the aspirator bottle.

Procedure

Acquisition of cocaine self-administration occurred under a fixed-ratio (FR) 1 schedule with 12-h access to 0.2 mg/kg cocaine. Experimental sessions began at 1000 hours each morning. A food hopper placed above the active response lever, as well as a food pellet taped to the lever were initially used to facilitate drug self-administration. Once animals were reliably self-administering at least 100 infusions of cocaine per day, the daily food allotment was decreased to 20 g, obtainable through food receptacles recessed into one wall of the chamber. Access to cocaine was gradually decreased from 12 to 2 h, over an average of 25.4 (±4.6) days. The dose of cocaine was gradually increased from 0.2 to 0.4 mg/kg over an average of 17.3 (±1.8) days or from 0.4 to 1.0 mg/kg over an average of 13.2 (±2.5) days. Rats ultimately had access to cocaine during the initial 2 h of a 7-h session under a FR 1 schedule (see Fig. 1). At the beginning of the 3rd hour, the cocaine infusion pump and the tubing up to the swivel were changed and saline was made available for the remaining 5 h of the session. The 3rd hour was when most of the extinction responding occurred. After the 7-h session ended, automatic infusions of saline were delivered every 30 min to prevent occlusion of the catheter, but lever-press responses had no programmed consequences during the 17-h intersession period. Before the start of the experimental session, the saline pump was exchanged for a cocaine pump and cocaine was made available for the first 2 h of the session. Thus, pumps were changed immediately before the start of the session and 2 h after the start of the session.

When the saline pump was replaced by the cocaine pump at the start of the session, the saline in the "dead" space between the swivel and the rat was not cleared. Thus, the first three to four infusions during the 1st hour of the session delivered saline to the rat instead of cocaine. Similarly, when the cocaine pump was replaced by saline at the beginning of the 3rd hour of the session, the cocaine in the dead space was not cleared and so the first three to four infusions during the 3rd hour of the session delivered cocaine instead of saline. Although it would have been preferable to clear the dead space when pumps were changed, the required disconnection of the cannula fittings would have increased the chance of introducing air and/or bacteria to the catheter system, thereby shortening catheter life by increasing the probability of clotting and infection.

Priming injections

Rats received an experimenter-administered priming injection of either saline or cocaine (0.32, 1.0 or 3.2 mg/kg IV) at the beginning of the 4th hour of the session. The volume of drug administered was between 0.1 and 0.5 ml, followed by a 0.5-ml saline flush to ensure that the entire cocaine dose was delivered to the rat. A saline injection of approximately equal volume was administered by the experimenter at the beginning of the 4th hour on days when test drugs were not administered. Priming injections were administered in nonsystematic order. At least 2 days of stable behavior elapsed between priming injections of cocaine.

Feeding conditions

Rats were maintained under three different food levels: one group was given 8–12 g food to maintain body weight at 80% of free-feeding weight, a second group was given 20 g food per day, and a third group was given unlimited access to food. Rats with unlimited access to food ate an average of 24.5 (±0.6) g food per day. Under each condition, rats were fed either 30 min prior to the start of the session or at the end of the 7-h session. Although priming doses were administered in nonsystematic order, each priming injection was administered when rats were fed before the session and then, on a separate day, when rats were fed after the session. The next priming dose was then administered, again when rats were fed before and then after the session. On days when priming doses were not administered, rats were fed before the start of the experimental session. Thus, the effects of acute (before versus after session feeding) and chronic (8–12 g versus 20 g versus unlimited food) deprivation were evaluated.

Approximately every 5th day, sodium methohexital (1.25 mg/kg IV) was administered intravenously to check catheter patency. A catheter was considered patent if the rat was immediately anesthetized following administration of sodium methohexital. If the catheter was not patent, a new catheter was implanted into the right jugular vein or a leaking cannula connection was repaired, and the experiment was resumed after the animal recovered from surgery and baseline levels of cocaine, food and water intake had been re-established. Methohexital injections were scheduled so as not to interfere with experimental protocols.

Data analysis

A repeated measures analysis of variance (ANOVA) was used to evaluate the effects of the independent variables (amount of food available, time of feeding, cocaine priming dose, and cocaine maintenance dose) on the number of infusions self-administered during the experimental session (see Table 1 for a summary of the experimental design). Identical analyses were conducted to evaluate the number of responses on the inactive lever. Five groups of rats were used to complete the study. Due to catheter failure, only a subset of rats in each group received all of the cocaine priming injections. Therefore, only data from those rats that received all of the cocaine priming injections were analyzed for the hour 4 data. In the first analysis (data shown in Fig. 2, left column), the effects of cocaine maintenance dose, time of feeding, and session hour on the number of infusions self-administered were analyzed in rats that received cocaine maintenance doses of 0.2, 0.4, or 1.0 mg/kg

Table 1 Experimental design

Group	Cocaine maintenance dose mg/kg)	Food	*n* (h 1, 2, 3)	*n* (h 4)
1	0.2	8–12 g	5	4
2	0.4	8–12 g	5	5
3	0.4	20 g	6	4
4	0.4	Unlimited	5	4
5	1.0	8–12 g	6	5

during hours 1 and 2, and saline infusions during hour 3. Maintenance dose was a between-subjects variable, while time of feeding (8–12 g before versus after) and session hour (1, 2, and 3) were within-subjects variables. In the second analysis (data shown in Fig. 2, right column), the effects of cocaine maintenance dose (0.2, 0.4, or 1.0 mg/kg), time of feeding (8–12 g before versus after) and cocaine priming dose (saline, 0.32, 1.0, 3.2 mg/kg) on the number of saline infusions self-administered during hour 4 of the session were evaluated. Maintenance dose was a between-subjects variable, and both time of feeding and cocaine priming doses were within-subjects variables. In the third analysis (data shown in Fig. 3, left column), the effects of amount of food available, time of feeding, and session hour on the number of infusions self-administered were analyzed in rats that received a cocaine maintenance dose of 0.4 mg/kg. The amount of food available (8–12 g, 20 g, or unlimited access) was a between-subjects variable, while time of feeding (before versus after) and session hour (1, 2, and 3) were within-subjects variables. In the fourth analysis (data shown in Fig. 3, right column), the effects of the amount of food available (8–12 g, 20 g, or unlimited access), time of feeding (before versus after), and cocaine priming dose (saline, 0.32, 1.0, 3.2 mg/kg) on the number of infusions self-administered during hour 4 were evaluated. The amount of food available was a between-subjects variable, while time of feeding and cocaine priming dose were within-subjects variables. For comparison purposes, data from group 2 (0.4 mg/kg cocaine, 8–12 g food) were presented in Fig. 2 (middle row) as well as in Fig. 3 (top row). A level of $P<0.05$ was used to indicate statistical significance.

Results

Figure 2 (left column) shows the mean number of infusions self-administered during hours 1 and 2 of the experimental session when 0.2 (upper panel), 0.4 (middle panel), or 1.0 (lower panel) mg/kg cocaine was available. Responding on the active lever during hour 3 resulted in saline, instead of cocaine, deliveries. Rats in each cocaine dose group were fed 8–12 g food either immediately before or after the 7-h session. During hours 1 and 2, rats self-administering the lowest dose of cocaine (0.2 mg/kg) received an average of 39.7 (±5.5) infusions per hour. The number of infusions self-administered during hours 1 and 2 by rats receiving 0.4 and 1.0 mg/kg cocaine progressively decreased to 28.5 (±3.6) and 12.2 (±2.3) per hour, respectively. Although the number of infusions decreased with increases in maintenance dose, the total amount of cocaine that was self-administered increased with increases in maintenance dose: rats self-administered a total of 7.9, 11.4 or 12.2 mg/kg cocaine during hours 1 and 2 when the maintenance dose was 0.2, 0.4 or 1.0 mg/kg, respectively. The main effect of cocaine maintenance dose was statistically significant [$F(2, 13)=6.5$, $P<0.05$]: the mean number of infusions

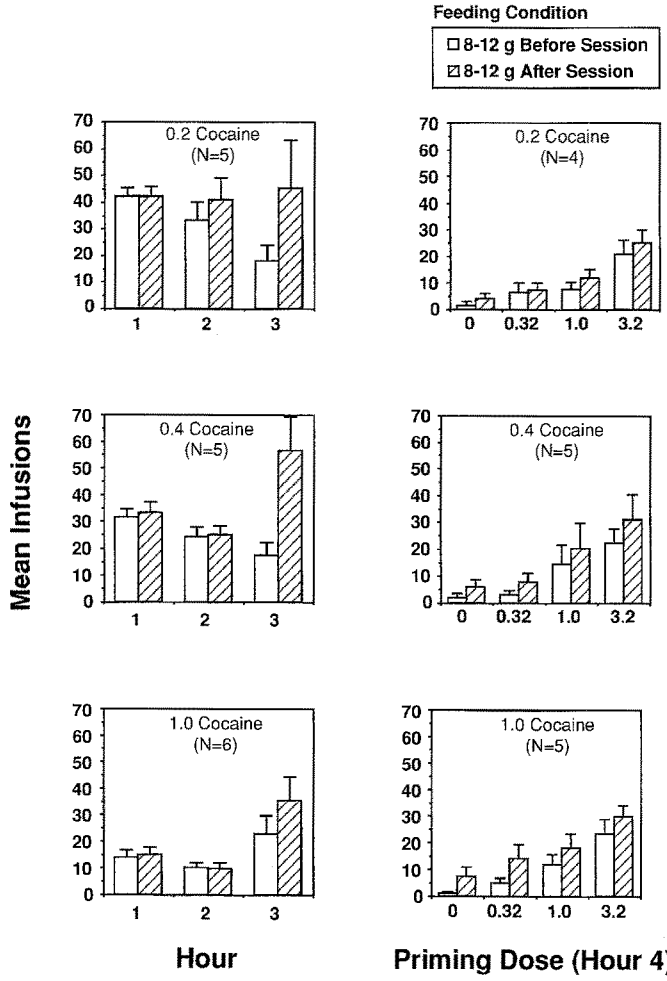

Fig. 2 *Left panels*: pattern of responding when either cocaine (hours 1 and 2) or saline (hour 3) was available in the infusion pumps. *Right panels*: reinstatement of responding produced by a priming injection of either saline (0) or cocaine (0.32, 1.0, or 3.2 mg/kg, IV) administered at the beginning of the 4th hour when saline was available in the infusion pumps. Each bar represents the mean number of infusions delivered when 0.2 (*upper panel*), 0.4 (*middle panel*), or 1.0 (*lower panel*) mg/kg was available during the first 2 h of the session. Rats were fed 8–12 g food either before (*open bars*) or after (*striped bars*) the 7-h session. Data represent means averaged across rats. Error bars represent±1 SEM

self-administered by rats receiving 0.2 mg/kg cocaine was significantly greater than the number of infusions self-administered by rats receiving 1.0 mg/kg [$F(1, 13)=12.1$, $P<0.05$], but not 0.4 mg/kg.

The main effect of hour was significant [$F(2,26)=3.5$, $P<0.05$], as was the main effect of time of feeding [$F(1,13)=11.7$, $P<0.05$]. The interactions between hour and cocaine doses [$F(2,26)=3.4$, $P<0.05$], and hour and time of feeding [$F(2,26)=33.4$, $P<0.05$] were also statistically significant. However, the interaction between time of feeding and cocaine doses was not statistically significant. Collapsing across cocaine doses, the number of infusions self-administered during the first 2 h of the session (when cocaine was available) was not significantly different when rats were fed either before or after the session. Rats fed before the session self-administered

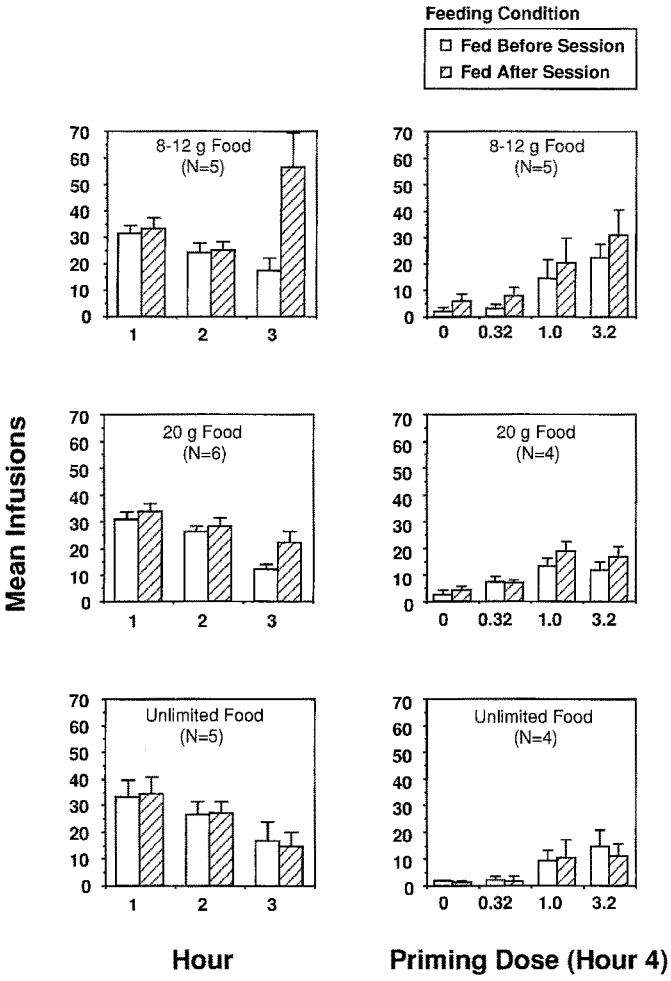

Fig. 3 *Left panels*: pattern of responding when either 0.4 mg/kg cocaine (hour 1 and 2) or saline (hour 3) was available in the infusion pumps. *Right panels*: reinstatement of responding produced by a priming injection of either saline (0) or cocaine (0.32, 1.0, or 3.2 mg/kg, IV) administered at the beginning of the 4th hour when saline was available in the infusion pumps. Each bar represents the mean number of infusions delivered when either 8–12 g (*upper panel*), 20 g (*middle panel*), or unlimited (*lower panel*) food was available either before (*open bars*) or after (*striped bars*) the 7-h session. Data represent means averaged across rats. Error bars represent ±1 SEM

significantly fewer infusions during the 2nd hour that cocaine was available, compared to the 1st hour [$F(1,26)=7.5$, $P<0.05$]. During hour 3 (when saline was available), the mean number of infusions more than doubled when rats were fed after the session [$F(1,26)=115.6$, $P<0.05$], compared to before-session feeding. However, responding on the inactive lever during hour 3 was also significantly greater when feeding occurred after, compared to before, the session [$F(1,26)=14.5$, $P<0.05$; data not shown].

Figure 2 (right column) shows the number of saline infusions self-administered during hour 4 when a priming dose of cocaine (0.0, 0.32, 1.0, or 3.2 mg/kg) was administered at the beginning of the 4th hour when rats were fed either before or after the session. Priming doses were administered to rats maintained on 0.2, 0.4 or 1.0 mg/kg cocaine during hours 1 and 2, although in hour 4 they were maintained on saline. The main effect of cocaine maintenance dose was not statistically significant, and the interaction between cocaine maintenance dose and priming dose was also not statistically significant. However, the main effect of priming dose was significant [$F(3,33)=28.2$, $P<0.05$]. A dose-related increase in the number of infusions that were self-administered occurred as a result of the cocaine priming injections, compared to priming injections of saline. Collapsing across cocaine maintenance dose and time of feeding, priming doses of 1.0 [$F(1,33)=16.4$, $P<0.05$] and 3.2 [$F(1,33)=73.1$, $P<0.05$], but not 0.32, resulted in the self-administration of significantly more infusions than after a saline priming dose. The main effect of time of feeding was also significant [$F(1,11)=13.0$, $P<0.05$]: rats self-administered significantly more infusions during the 4th hour when they were fed after the session, compared to before the session. The number of infusions self-administered during hour 5 was also higher when rats were fed after, compared to before, the experimental session (data not shown). Responding during hours 6 and 7 was generally near-zero, so the data from hours 6 and 7 will not be discussed further. The interactions between time of feeding and cocaine maintenance dose, as well as time of feeding and priming dose, were not statistically significant. The main effects of cocaine maintenance dose, time of feeding, and priming dose were not statistically significant for responses on the inactive lever during hour 4.

Figure 3 (left column) shows the mean number of infusions self-administered during hours 1, 2, and 3 in rats self-administering 0.4 mg/kg cocaine when they were fed either 8–12 g food (upper panel) or 20 g food (middle panel), or had unlimited access to food (lower panel). The main effect of food groups (8–12, 20, or unlimited) was not statistically significant: during hours 1 and 2, rats self-administered approximately 25–30 infusions regardless of the amount of food available. However, the main effect of hour was significant [$F(2,26)=22.9$, $P<0.05$]: rats self-administered significantly more infusions during hour 1 than during hour 2 or 3. The main effect of time of feeding was also significant [$F(1,13)=11.1$, $P<0.05$], as were the interactions between time of feeding and food group [$F(2,13)=4.5$, $P<0.05$], time of feeding and hour [$F(2,26)=19.7$, $P<0.05$], and hour and food group [$F(4,26)=16.8$, $P<0.05$]. During hours 1 and 2, rats in all food groups self-administered slightly more infusions when fed after the session than when fed before the session. During hour 3, when saline replaced cocaine in the infusion pumps, the number of infusions self-administered increased dramatically in rats that were fed 8–12 g food after the session, increased slightly in rats that were fed 20 g, and did not increase at all in rats with unlimited access to food. The main effect of hour was also statistically significant for responses on the inactive lever [$F(2,26)=5.7$, $P<0.05$]: responses were significantly greater during hour 3 compared to hour 1 [$F(1,26)=5.6$, $P<0.05$] or 2 [$F(1,26)=10.7$, $P<0.05$]. However, the main effects of food groups and time of

feeding were not statistically significant for responses on the inactive lever.

Figure 3 (right column) shows the mean number of saline infusions self-administered during hour 4 in rats tested under the three food levels (8–12 g, 20 g, or unlimited) and a maintenance dose of 0.4 mg/kg cocaine. A priming injection of cocaine (0.0, 0.32, 1.0, or 3.2 mg/kg) was administered at the beginning of the 4th hour when food was given either before or after the experimental session. The main effect of cocaine priming dose was statistically significant [$F(3,30)=16.2$, $P<0.05$]: collapsing across food levels and time of feeding, priming doses of 1.0 [$F(1,30)=20.2$, $P<0.05$] and 3.2 [$F(1,30)=34.5$, $P<0.05$], but not 0.32, resulted in the self-administration of significantly more infusions than a priming dose of saline. However, the main effects of food group and time of feeding were not statistically significant for responses on the active lever, nor were any of the interactions statistically significant. The main effects of food groups, priming dose and time of feeding were also not statistically significant for responses on the inactive lever.

Discussion

The pattern of cocaine self-administration as a function of maintenance dose described here has been reported previously in rats self-administering IV morphine (Smith et al. 1976), etonitazene (Carroll and Boe 1984), or cocaine (Carroll and Lac 1992), and appears to be a general phenomenon in IV drug self-administration experiments. Namely, the number of cocaine infusions that were self-administered during hours 1 and 2 decreased with increases in maintenance dose (0.2, 0.4, or 1.0 mg/kg cocaine), but the total amount of cocaine that was self-administered increased. In contrast, extinction responding during hour 3 was similar regardless of cocaine maintenance dose. An earlier study examining the effects of maintenance dose on the pattern of extinction responding in rats trained to self-administer different doses of amphetamine IV showed that while the number of responses to extinction was not different as a function of maintenance dose, the time to extinction was greater in rats self-administering higher doses of amphetamine (Yokel and Pickens 1976). In the present study, the number of infusions during hour 3 was approximately one-half, two-thirds, and double the number of infusions self-administered during hours 1 and 2 in rats maintained on 0.2, 0.4, and 1.0 mg/kg cocaine, respectively.

When rats were fed 8–12 g food before versus after the experimental session, self-administration during hours 1 and 2 was not changed. The lack of increase in cocaine self-administration during hours 1 and 2 was inconsistent with a number of studies showing that drug self-administration is increased following food deprivation conditions (e.g., Carroll and Meisch 1984). One variable that may have contributed to the difference between these earlier studies and the present one was the fact that rats typically had 24-h access to cocaine in the previous studies, and only 2-h access in the present experiment. Two hours may not be a sufficient amount of time for feeding effects on cocaine self-administration to become apparent. One study showed that the number of responses in rats with 24-h access to cocaine was similar under food satiation and deprivation conditions during the first few hours of the session, and that increases in responding in food deprived rats did not occur for at least 8 h (Carroll et al. 1981). Furthermore, although rats were chronically maintained under relatively stringent food deprivation conditions (8–12 g food), the before-session versus after-session feeding conditions represented only a 7-h difference in time of feeding. Thus, if rats were food deprived for a longer period of time, increases in cocaine self-administration behavior during hours 1 and 2 may have been observed.

Although self-administration during hours 1 and 2 did not change when rats were fed before versus after the session, extinction responding during hour 3 increased when rats were fed after the session. There were no systematic increases as a function of cocaine maintenance dose in the number of infusions self-administered during hour 3 when rats were fed after the session. Given that responding on the inactive lever during hour 3 was significantly greater than hours 1 or 2, the increase in responding during hour 3 may simply reflect a general increase in activity in these rats. During hour 4, priming doses of cocaine produced a dose-related increase in reinstatement of responding. These results were similar to previous experiments showing that the magnitude of responding increased with increases in the cocaine priming dose (de Wit and Stewart 1981; Comer et al. 1993). In addition to priming injections of drugs, other stimuli such as electrical brain stimulation also appear to increase reinstatement of operant responding, and the magnitude of this increase varies as a function of the intensity of the stimulus (for discussion, see Stewart and de Wit 1987). The fact that the magnitude of the reinstatement of responding was consistently greater when rats were fed after the session compared to before the session suggests that in addition to the intensity of the stimulus, food deprivation is another important variable that modifies relapse-like behavior. These results suggest that extinction responding, which may be viewed as a model for drug craving, as well as reinstatement of responding, or relapse-like behaviors, are more sensitive than drug self-administration to interoceptive stimuli.

While the number of infusions self-administered during hours 1 and 2 varied with cocaine maintenance dose, it did not vary with changes in the daily food allotment: rats self-administered approximately the same amount of cocaine (0.4 mg/kg) during hours 1 and 2 whether they were maintained on 8–12 g, 20 g, or unlimited food. Extinction responding during hour 3 was also similar in all three food groups when rats were fed before the session. However, the 8- to 12-g food group emitted dramatically more responses when fed after the session, the 20-g food group emitted slightly more responses, and the unlimited

food group emitted the same number of responses when fed after, compared to before the session. Thus, acute changes in time of feeding had a much greater effect on responding in rats that were maintained on the least amount of food.

The mechanism(s) by which food deprivation alters these behaviors is unclear based on the results of the present study, although several explanations for these results are possible. The interaction between reinforcers has been cited as an important variable in drug-taking behaviors. For example, a recent study demonstrated that acquisition of cocaine self-administration was either reduced or completely eliminated in rats with concurrent access to a glucose and saccharin solution (Carroll and Lac 1993). In addition to altering acquisition of drug self-administration, concurrent access to a sweet solution coincided with a decrease in cocaine intake in both rats and rhesus monkeys maintained on cocaine (Carroll et al. 1989; Comer et al. 1994). Human drug abusers who were offered alternative reinforcers as incentives for continuing abstinence also remained drug-free for a longer period of time than those who received drug counseling but no incentives (Higgins et al. 1991, 1993). Conversely, when subjects are deprived of alternative reinforcers, such as a sweetened solution, drug intake increases (Carroll et al. 1989). Thus, it may be that by depriving rats of an alternative reinforcer (i.e., food), drug-seeking behavior increases. The fact that reinstatement of responding increased when rats were fed after the session could be due to the fact that under acute food deprivation conditions, the salience of the interoceptive stimuli produced by cocaine increased so that responding increased after a priming injection. In conclusion, although cocaine dose is an important variable in maintenance responding, its effects on extinction and reinstatement of responding are much less robust. In contrast, both acute and chronic food deprivation affect extinction and reinstatement of responding.

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