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ENHANCEMENT BY PRE-SESSION FEEDING OF THE EFFECTS OF COCAINE ON FOOD-REINFORCED LEVER PRESSING OF RATS[1]

SESIONES DE PRE-ALIMENTACIÓN AUMENTAN LOS EFECTOS DE LA COCAINA SOBRE LA CONDUCTA DE PRESIONAR UNA PALANCA EN RATAS REFORZADA CON COMIDA

MARK A. MILLER
DAVID W. SCHAAL
WEST VIRGINIA UNIVERSITY[2]

ABSTRACT

Lever pressing of rats deprived to 80% of their free-feeding weights was maintained on a fixed-ratio 30 schedule of food reinforcement. The experimental session was composed of five, 3-min periods in which the houselight was on and the fixed-ratio 30 schedule was in effect alternating with five, 6-min black-out periods during which responding was not reinforced. When rates of pressing during lights-on periods were stable, cocaine was administered at the start of each blackout period. Cumulative doses received were 3.0, 5.6, 10.0, 17.0, and 30.0 mg/kg. In other test sessions, saline was administered at the start of each blackout. The effects of saline and cocaine administration were determined under two deprivation conditions. In one, rats were fed either 10.0 g or 5.0 g of rat chow 2 hrs prior to the session. In the other, rats were handled identically but received no food. When no pre-session feeding occurred, saline administration slightly

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2. Department of Psychology, West Virginia University. Send correspondence to: David W. Schaal, West Virginia University, PO Box 6040, Morgantown, WV, 26506-6040, phone: (304) 293-2001 ext. 603, fax: (304) 293-6606, e-mail: dschaal@wvu.edu.

increased response rates of some rats. Cocaine generally produced dose-dependent decreases in rates and did so at lower doses when rats had been pre-fed compared to when they had not. Thus, pre-session feeding made response rates more sensitive to the rate-reducing effects of cocaine.

Key words: Pre-feeding, fixed-ratio, cocaine, lever-pressing, rats.

RESUMEN

Ratas mantenidas al 80% del peso que mostraron en alimentación libre, respondieron a una palanca para obtener comida de acuerdo a un programa de reforzamiento de Razón-Fija 30. La sesión experimental tenía cinco periodos de 3 minutos con una luz general encendida y el programa de Razón-Fija 30 en efecto. Estos periodos alternaron con otros seis periodos de 6 minutos de obscuridad total en los cuales las presiones de palanca no recibieron reforzamiento. Cuando las tasas de respuesta se estabilizaron en los periodos de luz, a las ratas se les administró cocaína en los periodos de obscuridad. Las dosis acumuladas que recibieron fueron de 3.0, 5.6, 10.0, 17.0 y 30.0 mg/kg. En otras sesiones de prueba, se administró una solución de agua salina durante los periodos de obscuridad. Tanto los efectos de la administración de cocaína, así como los de la administración de agua salina, se evaluaron bajo dos condiciones diferentes de privación de alimento. En una condición las ratas recibieron 10.0 g, o bien 5 g de Purina Chow dos horas antes de la sesión experimental. En la otra condición las ratas no recibieron comida antes de la sesión, pero se les trató y manipuló de la misma manera que si la hubiesen recibido. Cuando las ratas no fueron pre-alimentadas, la administración de salina produjo un leve incremento en las tasas de respuesta. La cocaína generalmente produjo decrementos en tasa de respuestas dependientes de la dosis administradas. Con dosis bajas de cocaína la pre-alimentación también causó decrementos en la tasa de respuestas, pero esto no ocurrió cuando las ratas no fueron pre-alimentadas. Por tanto, las sesiones de pre-alimentación causaron que las tasas de respuesta fueran mas sensibles a los efectos de la cocaína.

Palabras clave: Pre-alimentación, razón-fija, cocaína, presión de palanca, ratas.

The effects of several drugs on food-maintained behavior have been shown to depend on level of food deprivation. The rate-reducing effects of cocaine (Schaal & Branch, 1992; Schaal, Miller, & Odum, 1995), *d*-amphetamine (Cole, 1967; Gollub & Mann, 1969; Sampson, 1986), methadone (Kelly & Thompson, 1988), and morphine (Odum, Haworth & Schaal, 1998) on food-reinforced behavior are lessened by more severe food deprivation. For example, Schaal and Branch (1992) tested the effects of cocaine on pigeon's key pecking under a fixed-ratio (FR) 30 schedule of food reinforcement when pigeons were maintained at 70%,

80% and 90% to 100% of their free-feeding weights. Cocaine reduced response rates in a dose-dependent manner. Reductions in response rates occurred at lower doses when pigeons were relatively less food deprived. Schaal et al. (1995) replicated this effect using a multiple FR 30 fixed-interval (FI) 5-min schedule of food reinforcement. Overall rates of pecking maintained by both FR and FI schedules were suppressed by lower doses of cocaine when pigeons were maintained at 82.5 to 85% of their free-feeding weights compared to when they were maintained at 70% of their free-feeding weights. In addition, the rate-increasing effect of cocaine on low-rate behavior during the early portion of the FI schedule was enhanced by more severe food deprivation.

In the experiments by Schaal and Branch (1992) and Schaal et al. (1995), pigeons' body weights were maintained relative to their free-feeding weights using what has become standard laboratory practice, i.e., feeding after sessions in order to maintain body weights at a stable level during entire conditions. The present experiment attempted to extend the findings of Schaal and Branch and Schaal et al. by assessing whether acute changes in level of food deprivation would alter the rate-reducing effects of cocaine. Acute changes in deprivation levels were arranged by feeding rats prior to some experimental sessions during which cocaine was tested.

METHOD

Subjects

Eight experimentally naïve male Sprague-Dawley rats, approximately 150 days old at the start of the experiment, were used. All rats were housed individually in a temperature-controlled colony room on a reversed 12-hr light/dark cycle (lights were off from 5:00 a.m. to 5:00 p.m.). Rats were maintained at 80% of their free-feeding weights and were allowed free access to water in their home cages. One rat was discarded from the study because its response rates were suppressed completely after every dose of cocaine, regardless of feeding conditions.

Apparatus

Four custom-built operant chambers, 28.5 cm long, 25 cm wide and 20 cm high, were used. The side walls and ceiling were constructed of Plexiglas, and the front and rear walls were aluminum. The grid floor (Coulbourn Instruments, Model E10-10SF) was constructed of stainless steel rods 0.5 cm in diameter and spaced 1.5 cm apart. Two aluminum levers, spaced 13.5 cm apart and 5 cm from the floor, were mounted on the front wall. The levers required 0.25 N to operate. A 28-V dc houselight was mounted 2 cm above the chamber near the front wall between the levers. Twenty-eight-V dc lamps, covered with white plastic caps, were located 5

cm above each lever. Forty-five mg Noyes pellets were made available using a Coulbourn model E14-12 pellet dispenser. The pellets were delivered into a stainless steel pan mounted behind a round aperture 3.5 cm in diameter and centered 5 cm from each lever. The chambers were housed in sound-attenuating enclosures equipped with ventilation fans. White noise was used to mask extraneous sounds. Contingencies were programmed and data were recorded using MedState Notation® software and a Med-PC computer interface system (MED Associates & Tatham, 1991).

Procedure

Baseline. Sessions were conducted daily at approximately the same time. Initially, each rat received magazine training, which consisted of placing the rat in the chamber with the houselight on and delivering food pellets response independently. After rats reliably ate the food pellets when delivered, presses on the left lever were shaped via the method of successive approximations. During shaping, the houselight and the lamp above the left lever were on. The number of presses required to produce a food pellet was increased until a fixed-ratio (FR) 30 schedule was reached. As soon as lever pressing was maintained on the FR 30 schedule, it was changed to a multiple FR 30 Extinction schedule of food presentation. That is, five, 6-min black-out periods (i.e., all lights in the chamber were off) in which lever pressing was not reinforced alternated with five, 3-min periods in which the houselight and left lever lamp were on and the FR 30 schedule was in effect. Occasionally during these baseline sessions, rats were lifted from the chamber and then replaced at the beginning of each black-out period. This was intended to habituate them to handling during experimental sessions.

Cumulative dosing and pre-session feeding procedures. When baseline response rates became stable and there were no systematic changes in response rates across successive FR periods (judged by visual inspection), tests of cocaine or saline began. Cocaine hydrochloride (National Institute of Drug Abuse) was dissolved in sterile 0.9% saline and injected intraperitoneally in a volume of 0.5 ml/kg of the rat's 80% free-feeding weight. During cocaine test sessions, cocaine was administered at the start of each black-out period (3.0, 2.6, 4.4, 7.0, and 13 mg/kg respectively). This resulted in cumulative doses of 3.0, 5.6, 10.0, 17.0, and 30.0 mg/kg. During saline test sessions, equal volumes of saline were administered at the start of each black-out period. After injections, rats were immediately placed back into their chamber and the door was closed. At least 5 baseline sessions intervened between each administration of cocaine and saline.

The effects of saline and cocaine administration were determined under two food-deprivation conditions. Table 1 shows the order of exposure to each of the 4 experimental conditions for all rats. In one, the pre-session feeding condition, rats were placed in individual plastic tubs with free access to water and were fed either 5.0 or 10.0 g of rat chow 2 hr prior to the session. In the other, the no pre-session

feeding condition, rats were placed in the tubs 2 hr prior to the experimental session but received no food. Following this 2-hr period, the rats were given the initial injection of either saline or cocaine and were placed in their experimental chamber.

Table 1
Order of exposure to each of the experimental conditions for all subjects

Subject	Pre-fed + saline[a]	Pre-fed + cocaine	Not pre-fed + saline	Not pre-fed + cocaine
R1	1^{st}, 6^{th}	2^{nd}, 7^{th}	4^{th}, 8^{th}	3^{rd}, 5^{th}
R2	1^{st}, 6^{th}	2^{nd}, 7^{th}	4^{th}, 8^{th}	3^{rd}, 5^{th}
R3	1^{st}, 6^{th}	2^{nd}, 7^{th}	4^{th}, 8^{th}	3^{rd}, 5^{th}
R4	1^{st}, 6^{th}	2^{nd}, 7^{th}	4^{th}, 8^{th}	3^{rd}, 5^{th}
E1	3^{rd}, 6^{th}	4^{th}, 8^{th}	1^{st}, 5^{th}	2^{nd}, 7^{th}
E3	3^{rd}, 5^{th}	4^{th}, 8^{th}	1^{st}, 6^{th}	2^{nd}, 7^{th}
E4	3^{rd}, 6^{th}	4^{th}, 8^{th}	1^{st}, 5^{th}	2^{nd}, 7^{th}

* Numbers depict order of event.

Rats R1, R2, R3, and R4 were exposed initially to several cumulative administrations of cocaine that are not shown. It was during these tests that the final range of doses (i.e., 3.0 to 30.0 mg/kg), the precise method of pre-feeding and pre-session handling, the interval between pre-session feeding and the experimental session, and the amounts of food were established. In essence, these rats participated in pilot experimentation prior to the study reported here. Rats R1, R2, R3, and R4 then experienced two more cumulative dose-effect determinations under the established procedures, and three more rats (E1, E2, and E3) were tested under these procedures without being subjected to the pilot tests. Rats R1, R2, R3, and R4 received 10 g of rat chow during all tests of cocaine and saline in combination with pre-feeding. Rats E1, E3, and E4 received 10 g of rat chow during their first tests of cocaine and saline in combination with pre-feeding and 5 g of rat chow during their second tests.

Data analysis. The effects of cocaine and saline on response rates under conditions with pre-session feeding and no pre-session feeding are presented graphically for each rat (see Figures 1 & 2). The effects of cocaine and saline administration were expressed as a proportion of the response rates obtained from 2 sessions prior to each cumulative drug administration or saline administration. This was done because baseline response-rates were considerably different for each rat (ranging from 70 to 200 responses per minute). Hereafter, the

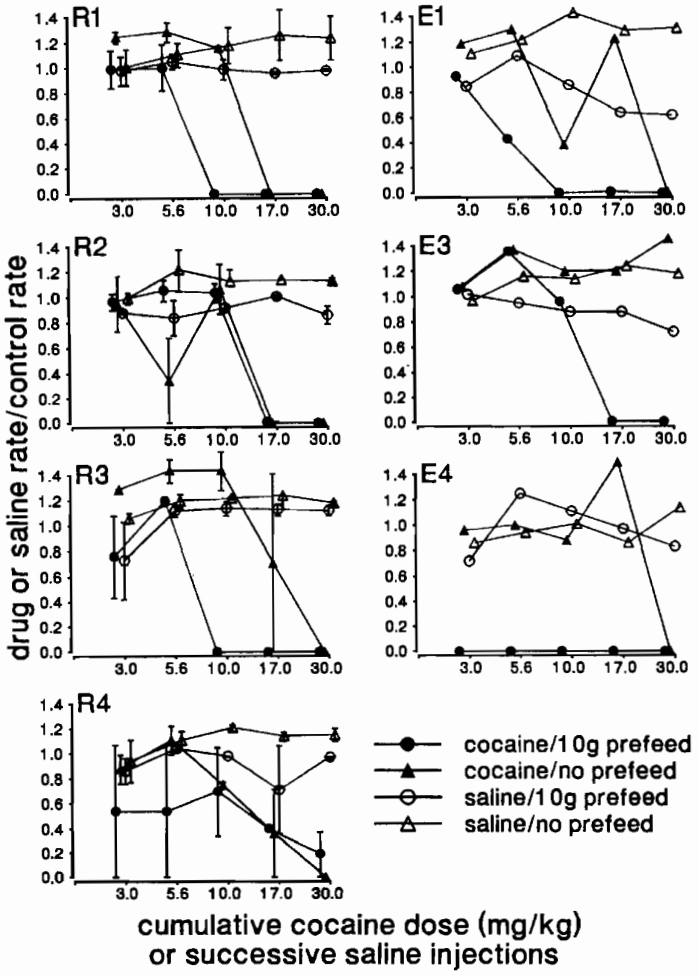

Figure 1. Effects of cocaine and saline on response rates. The effects are expressed as a proportion of the mean of the rates obtained from 2 sessions prior to each administration of cocaine and saline. Symbols in left panels represent means of two cumulative administrations of cocaine or successive saline injections (bar depict ranges), whereas in the right panels symbols represent single, cumulative administrations of cocaine or successive saline injections. Open triangles and open circles depict effects obtained after saline administration when rats were not pre-fed and when rats were pre-fed 10 g of food, respectively. Closed triangles and closed circles depict effects of cocaine after rats were not pre-fed and after rats were pre-fed 10 g of food, respectively.

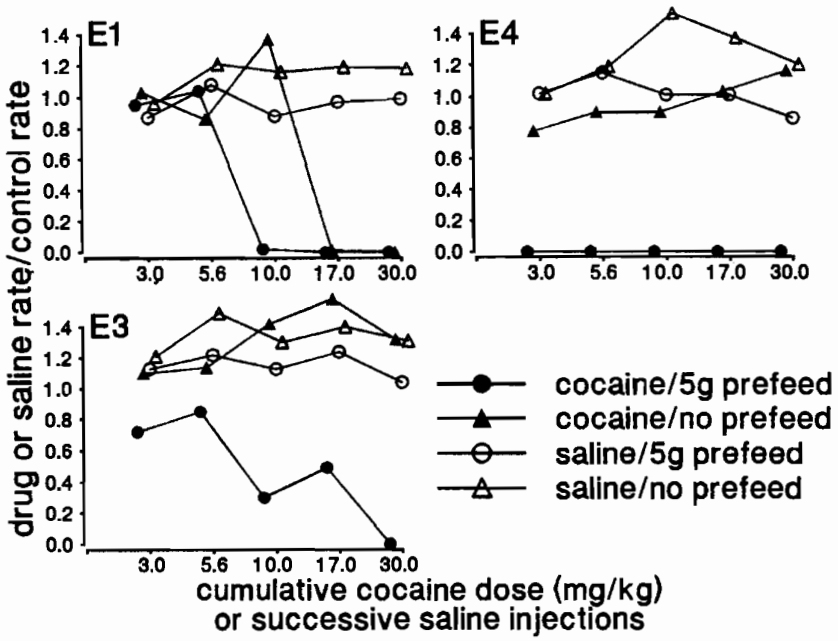

Figure 2. Effects of cocaine and saline on response rates. Other details are as in Fig. 1 except that the pre-session feeding amount was reduced to 5 g of food.

response rates obtained from 2 sessions prior to cocaine or saline administration will be referred to as control response rates.

Parametric tests were conducted. The effects of cocaine dose (3.0, 5.6, 10.0, 17.0, and 30.0 mg/kg) on response rates obtained under the feeding conditions that all 7 rats experienced (0 versus 10 g rat chow) were pooled across subjects and analyzed using a two-way repeated measures analysis of variance. Because Rats R1, R2, R3, and R4 were exposed to each experimental condition twice, the 2 response rates obtained for each experimental condition were averaged into 1 score for each condition for each rat. This was done in order to obtain an equal number of scores in each cell in the analysis of variance (n=7). Based on previous research (Schaal & Branch, 1992; Schaal et al., 1995), it was predicted that cocaine would suppress rates of lever pressing at a lower dose under the 10 g pre-session feeding condition compared to the 0 g pre-session feeding condition. Planned comparisons were used to test this prediction. Tests for differences in response rates under the 2 pre-session feeding conditions (0 versus 10g) occurred for each dose of cocaine.

The effects of saline injection (1^{st}, 2^{nd}, 3^{rd}, 4^{th}, and 5^{th} injection) on response rates obtained under the feeding conditions that all 7 rats experienced (0 versus 10 g rat chow) were pooled across subjects and analyzed using a two-way repeated measures analysis of variance. The data were aggregated in the same manner as in the analysis of cocaine's effects.

RESULTS

The effects of saline on response rates following pre-feeding of 10 g or no pre-feeding are depicted by unfilled symbols for each rat in Figure 1. The effects of cocaine and saline are expressed as a proportion of control response rates. The data points in the left panels (for Rats R1, R2, R3, and R4) represent means of two cumulative administrations of cocaine or successive saline injections (bars depict ranges). The points in the right panels (for Rats E1, E3, and E4) represent a single, cumulative administration of cocaine or successive saline injections. Slight increases in response rates can be seen for Rats R1, R3, E1, and E3 when saline was administered with no pre-feeding. Pre-feeding with 10 g of food reduced rates slightly following saline administration for Rats R2, R4, E1, and E3.

The effects of cocaine on response rates under each feeding condition are also shown in Figure 1 (see filled symbols). Cocaine decreased response rates in a dose-dependent manner under both food deprivation conditions for Rats R1, R2, R3, R4, and E1. Rat E3's response rates were not reduced at any dose tested when it was not pre-fed. Response rates were completely suppressed at all doses tested when Rat E4 was pre-fed 10 g. Response rates were reduced by lower doses when rats were pre-fed 10 g of food relative to when they had not been pre-fed for Rats R1, R3, E1, E3, E4, and at the lower doses for R4.

Figure 2 shows the effects of cocaine and saline on response rates for Rats E1, E3, and E4 during sessions prior to which no pre-feeding or pre-feeding of 5.0 g occurred. Response rates were slightly increased following saline injections and no pre-feeding for rats E3 and E4. Response rates were similar to control response rates following injections of saline and 5 g of pre-feeding. Cocaine reduced rates for at a lower dose for each rat when it was pre-fed compared to when it was not. When Rats E3 and E4 were not pre-fed, cocaine did not reduce response rates at any dose.

The effects of saline on response rates expressed as a proportion of control response rates across each successive FR 30 period under both pre-session feeding conditions (0 versus 10 g rat chow) were pooled across subjects and analyzed using a two-way repeated-measures analysis of variance. Saline injections generally increased response rates, $F(4,24) = 7.33$, p 0.01. Pre-feeding decreased response rates slightly, $F(1,24) = 14.42$, p 0.01. The effects of successive saline injections on response rates for the 2 pre-session feeding conditions are shown in the bottom panel of Figure 3. Response rates were slightly increased

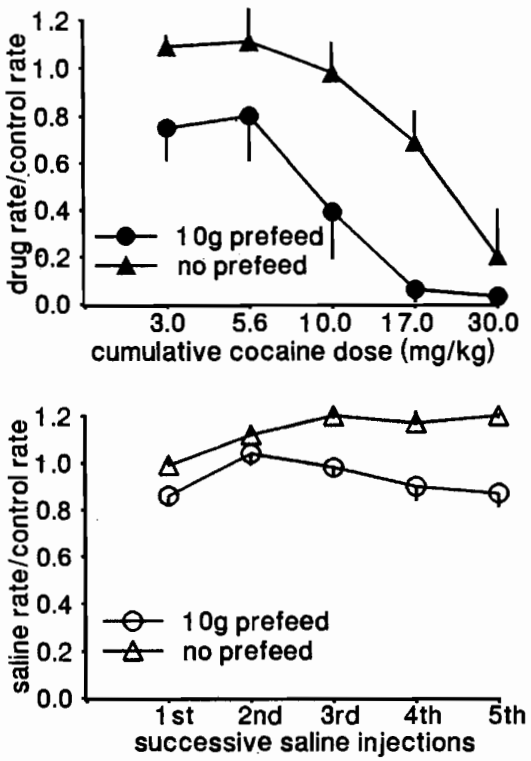

Figure 3. Averaged effects of cocaine and saline on response rates for the 2 pre-session feeding conditions. Top panel depicts effects of cocaine when rats were pre-fed 10 g (closed circles) and when rats were not pre-fed (closed triangles). Bottom panel depicts effects of saline when rats were pre-fed 10 g (open circles) and when rats were not pre-fed (open triangles). Bars represent standard errors.

across successive saline administrations for the no pre-session feeding condition (except for the 1st). Response rates were slightly decreased for the 10 g pre-session feeding condition (except for the 2nd injection). Post hoc tests confirm that the differences in response rates for the 2 pre-session feeding conditions for the 3rd, 4th, and 5th injections of saline were all significant ($p < 0.01$).

The effects of cocaine on response rates expressed as proportion of control response rates obtained under the 2 feeding conditions that all 7 rats experienced (0 versus 10 g rat chow) were pooled across subjects and analyzed using a two-way repeated-measures analysis of variance. Cocaine decreased response

rates dose-dependently, $F(4,24) = 13.26$, $p < 0.01$. Pre-feeding also reduced response rates, $F(1,24) = 10.7$, $p < 0.05$. The top panel in Figure 3 shows the effects of cocaine on response rates separated for the 2 pre-session feeding conditions. Mean response rates were clearly reduced at the 10.0 and 17.0 mg/kg doses after pre-feeding with 10 g of rat chow, whereas mean response rates were only slightly reduced when no pre-feeding occurred. Planned comparisons confirmed that the differences in response rates for the 2 pre-session feeding conditions at the 10.0 and 17.0 mg/kg doses of cocaine were significant ($p < 0.01$, respectively).

DISCUSSION

Response rates were increased slightly following saline injections, especially after the 3rd, 4th, an 5th injections, which may reflect an arousing effect of successive injections. This effect of successive saline injections, however, was not strong enough to override the rate-suppressive effect of pre-feeding with 10 g of food. Pre-feeding with 5 g of food did not decrease response rates (rates were actually increased for Rat E3). These findings are consistent with other studies demonstrating that food satiation decreases overall rates of food-reinforced responding in rats (Clark, 1958; Sidman & Stebbins, 1954; Heyman, 1993) and pigeons (Nevin, Mandell, & Yarensky, 1981). Cocaine reduced rates of lever pressing at lower doses for 5 of 7 rats when they were pre-fed 10 g compared to when they had not been pre-fed. Cocaine reduced rates of lever pressing at a lower dose for all 3 rats that were pre-fed with 5 g of food compared to when they were not pre-fed. Similar effects were observed using a more common laboratory procedure, in which different body weights were held stable for several weeks at a time while cocaine was tested (Schaal & Branch, 1992; Schaal et al., 1995). The present experiment extended the generality of those findings by showing that acute changes in food deprivation level could also alter the rate-reducing effects of cocaine.

Increased food deprivation has also been shown to lessen the rate-reducing effects of amphetamine in rats (Cole, 1967; Gollub & Mann, 1969; Samson, 1986), methadone in pigeons (Kelly & Thompson, 1988), and morphine in pigeons (Odum et al., 1998). Food deprivation also attenuates the rate-reducing effects of shock punishment in pigeons (Azrin, 1960), and in rats, food deprivation increases intracranial self-stimulation of the lateral hypothalamus (Carey, Goodall, & Lorens, 1975), shock-elicited aggression (Cahoon, Crosby, Dunn, Herrin, Hill, McGinnis, 1971), bar-pressing maintained by onset of a dim light (Davis, 1958), wheel-running (Sclafani & Rendel, 1978), and the reinforcing efficacy of wheel running (Pierce, Epling, & Boer, 1986). This variety of changes in behavior due to food deprivation suggests that the current results, which may be understood simply as the straightforward effect of lessening motivation, may actually reflect more general changes in behavior tied to food deprivation level.

The generality of the food-deprivation effect may be indicated most dramatically in the area of drug self-administration, where it has been shown that drug-reinforced behavior is enhanced by increasing food deprivation levels (Carroll & Meisch, 1984). This effect has been observed in rats and monkeys with cocaine and *d*-amphetamine (Carroll, France, & Meich, 1981; Carroll & Stotz, 1983; de la Garza, Bergman, & Hartel, 1981), etonitazene (Carroll & Meich, 1979), pentobarbital (Kliner & Meisch, 1982), phencyclidine and ketamine (Carroll & Meisch, 1980; Carroll & Stotz, 1983, 1984), ethanol (Meisch & Thompson, 1973; Oei & Singer, 1979), and delta-9-tetrahydrocannabinol (Takahashi & Singer, 1979, 1980). It is not clear why food deprivation alters drug-reinforced behavior in this manner, but there are possible explanations. For example, food deprivation may lessen the rate-suppressive effects of cumulative doses of self-administered drug. Rate-suppressive effects of self-administered drugs may account for the fact that responding maintained by relatively high doses of drug typically occurs at a lower rate than responding for lower, reinforcing doses (Downs & Woods, 1974; Woods, Winger, & France, 1987; Dworkin & Smith, 1988). When animals are more food deprived the rate-reducing effects of large, cumulative doses of self-administered drug may be lessened in a manner similar to food-reinforced responding in the present study, thereby increasing levels of self-administration. Researchers have suggested other explanations for this effect, most notably deprivation-induced enhancement of the reinforcing efficacy of drug (de la Garza & Johanson, 1987; Papasava & Singer, 1985; Takahashi & Singer, 1979) and the enhancement of the rate-increasing effects of drugs (Odum et al., 1998; Schaal et al., 1995). Thus, alterations by food deprivation of several behavioral effects of drugs may play a role in altering drug self-administration.

The ability of cocaine and other drugs to disrupt operant behavior may be related to the baseline strength of the behavior, strength here conceived in the manner suggested by Nevin (1974). In general, it is suggested that stronger behavior is more resistant to the disruptive effects of drugs. Results of several studies are consistent with this view. In the present study, responding may have been weakened by pre-feeding, thus enhancing the ability of cocaine to disrupt it. A similar logic applies to the results of studies showing similar effects (Odum et al., 1998; Schaal & Branch, 1992; Schaal et al., 1995). Response strength is most often manipulated by altering reinforcement rates (Nevin, Mandell, & Atak, 1983). In a study by Egli, Schaal, Thompson and Cleary (1992) it was shown that responding of pigeons maintained by relatively low reinforcement rates (arranged using variable-interval (VI) 75-s and 150-s schedules) was more easily suppressed by methadone and buprenorphine than responding maintained by relatively high reinforcement rates (VI 5-s and VI 10-s). Similar effects were obtained with cocaine under different-valued FR schedules (Hoffman, Branch, & Sizemore, 1987). More recently it was shown that lever pressing of rats maintained by an FR 50 schedule of food was more readily suppressed by cocaine when supplemental feeding occurred immediately after sessions compared to when it was delayed for

two hours, an effect that was also interpreted in terms of response strength (Ross & Schaal, in press). Although drug effects are not always consistently related to the baseline strength of behavior (Cohen, 1986), there are enough such effects to warrant continued research along these lines. It is possible that a theory of response strength may be an extremely important contribution of the experimental analysis of behavior to the understanding of the behavioral effects of drugs.

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