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Effects of amphetamine, dexfenfluramine, diazepam, and dietary manipulations on responding reinforced by stimuli paired with food in nonhuman primates

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Abstract

The purpose of this study was to determine how stimuli paired with food alters the effects of pharmacological and dietary manipulations on food intake. Responding of baboons was studied using a schedule of reinforcement that simulated food 'seeking' and food 'taking'. Under one condition, responding during the initial seeking component was reinforced by flashing lights that were paired with food delivery during the latter-taking component. Under another condition, responding during seeking components was reinforced by a 1-s time out that was paired with food delivery during the latter-taking component. Dexfenfluramine (DFEN) decreased responding within seeking and taking components under both conditions. Diazepam (DZP) increased responding within seeking and taking components under both conditions. Amphetamine (AMPH) increased responding within seeking components under the flashing-light condition, but did not alter responding within seeking components under the 1-s time-out condition. AMPH decreased responding within taking components under both conditions. As observed with AMPH, caloric prefeeding also increased responding within seeking components only under the flashing-light condition. As observed with DZP, acute deprivation also increased responding within seeking and taking components under both conditions. The effects of AMPH and caloric prefeeding on food seeking are dependent upon the type of stimuli, paired with primary reinforcement.

Keywords: Food intake; Baboon; Motivation; Deprivation; Amphetamine; Dexfenfluramine; Diazepam

1. Introduction

The probability that appetitive behavior will occur is determined by both the antecedents and consequences of that behavior (Mackintosh, 1974; Owen, 1980). Unfortunately, certain appetitive sequences related to one reinforcer can predominate over other appetitive sequences leading to behavioral disorders such as obesity, drug abuse and eating disorders (Levison et al., 1983; Mule, 1981). For many years, the search for effective behavioral and pharmacological treatments for these appetitive disorders has focused on altering the consequences of that behavior, such as decreasing the reinforcing effects of the abused commodity. The possibility that it is more difficult to stop a behavior after it has started than to prevent a behavior from occurring may play a role in the high-recidivism rates characteristic of appetitive disorders.

Within the last decade or so, it has become obvious that antecedent stimulus conditions can determine behavioral output. For example, data obtained in laboratory animals, using models of relapse, indicate that stimuli that have been paired with a commodity can elicit responding for that commodity and acquire conditioned reinforcing effects (e.g., Highfield et al., 2002; Woods and Winger, 2002). One model used to understand the complex effects of stimuli paired with primary reinforcement is based on the concept of incentive motivation: paired stimuli provide information about the likelihood that a commodity will soon be delivered and the potential reinforcing effects of that commodity (Bindra, 1978; Toates, 1981). The theoretical strength of these models is that stimuli are not viewed solely as conditioned stimuli, eliciting responses based on

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Pavlovian conditioning, but as stimuli whose effects are modulated by concurrent circumstances, for example, deprivation, as well as behavioral history.

Data obtained using laboratory rodents indicate that pharmacological manipulations can alter the incentive value of stimuli paired with reinforcement (e.g., Robinson and Berridge, 1993). Drugs that increase dopamine (DA) levels, such as amphetamine (AMPH), increase responding reinforced by conditioned reinforcers (e.g., Fletcher, 1995, 1996; Wyvell and Berridge, 2000), while drugs that increase serotonin (5-HT) levels, such as dexfenfluramine (DFEN), decrease responding reinforced by conditioned reinforcers (Fletcher, 1995, 1996; Wilson et al., 2000). A previous study from this laboratory (Foltin, 2001) reported similar findings using baboons.

In that study, the operant behavior of baboons was studied under a schedule of reinforcement that simulated food 'seeking' and food 'taking' (e.g., Collier et al., 1977; Collier, 1983; Foltin and Fischman, 1988). Baboons had access to food under these conditions, 24 h each day. The initiation and termination of all components were determined by the baboon. Responding during the seeking component, reinforced by flashing lights paired with food, using a second-order schedule (Kelleher, 1966), provided a measure of incentive value (Berridge and Robinson, 1998); that is, increases in responding during seeking components reflected enhanced motivational effects, while decreases in responding during seeking components reflected decreased motivational effects of the paired stimuli.

Because the previous study from this laboratory (Foltin, 2001) used only a single type of stimulus condition, the purpose of the present study was to compare the effects of two stimulus conditions that varied in intensity. Under the first condition, 12 s of flashing lights and 18 s of darkness were paired with food delivery (Foltin, 2001), while under the second condition, only 1 s of darkness was paired with food delivery. It was hypothesized that AMPH would produce greater increases in responding maintained by the paired stimuli under the flashing-light condition.

2. Methods

2.1. Animals

Eight adult male baboons (*Papio cynocephalus anubis*), weighing 25.2 to 32.9 kg (Mean = 29.4 kg) at the start of the study, were individually housed in standard nonhuman primate cages (0.94 × 1.21 × 1.52 m high) at The New York State Psychiatric Institute. Body weights remained stable, or increased slightly over the study. The baboons had 7 to 16 years experience responding under FR schedules and had participated in another study on the effects of some of the same manipulations on responding maintained under a similar operant schedule (Foltin, 2001). The room was illuminated with fluorescent lighting from 0700 to 1900 h daily. In addition to food earned during experimental sessions, two chewable vitamins ("Kiddy Chews", Schein Pharmaceutical, Port Washington, NY), two pieces of fresh fruit (80–100 kcal each), and a dog biscuit (150 kcal, Old Mother Hubbard, Lowell, MA) were also given daily. Water was available ad libitum from a spout located at the back of each cage. All aspects of animal maintenance and experimental procedures complied with the U.S. National Institutes of Health Guide for Care and Use of Laboratory Animals, and was approved by the New York State Psychiatric Institute Animal Care and Use Committee.

2.2. Apparatus

A response panel holding from bottom to top, a food hopper, two Lindsley levers spaced 0.30 m apart (Gerbrands, Arlington, MA), four stimulus lights (two above each lever), and a pellet dispenser (BRS-LVE model PDC-005, Beltsville, MD) was attached to the front of each cage. All schedule contingencies were programmed using Pascal on Macintosh (Cupertino, CA) computers located, along with the interface, in an adjacent room.

2.3. Schedule of reinforcement

Responding under each component of a two-component chain schedule of reinforcement was on a separate response manipulandum. The first seeking component, signalled by a light above the left lever, was an FI 30-min schedule, with an FR 10 second-order component [FI 30′ (FR 10:S)]. Thus, after every 10th response during the FI component, the stimuli associated with reinforcer delivery during the second component were presented. The first FR 10 completed after 30 min resulted in the light above the left lever being extinguished, and the light above the right lever being illuminated, signalling the availability of reinforcement under the FR component of the chain schedule. There was a 10-min limited hold for the first component, such that after the expiry of the 30-min FI, the next FR 10 had to be completed within 10 min. Failure to complete an FR 10 within 10 min reset the schedule back to a 30-min seeking component. The second taking component of the chain schedule was maintained under an FR 10 schedule of food reinforcement (one grain-based 'dustless' banana-flavored 1-g food pellet; 3.34 kcal/g: 20.1% protein, 3.3% fat, 55.3% carbohydrate, 3.3% ash, < 5% moisture, and 4.0% fiber; Bio-serv, Frenchtown, NJ). After a 10-min interval, in which no responses occurred, the taking component terminated; that is, the duration of each taking component was determined by each baboon. The light above the right taking lever was then extinguished, and the light above the left seeking lever was again illuminated. To gain access to another taking component, the baboon was required to complete the response requirement of the seeking component again. This schedule was in effect 24 h/day, with the exception of a brief period during which the data were

backed-up and printed (approximately 5 min), which occurred at 0800 h each morning.

Responding was studied using two types of paired stimuli: flashing lights and 1-s time outs. Under the flashing-light condition, reinforcer deliveries during the taking component were paired with the flashing over a 12-s interval (1 s on: 1 s off), of all 4 stimulus lights above both levers, and an additional 18 s of darkness, when all stimulus lights were extinguished. Under the 1-s time-out condition, reinforcer deliveries during the taking component were accompanied by only 1 s of darkness, when all stimulus lights were extinguished. These stimuli were also presented after every 10th response during the FI-seeking component.

2.4. Procedure and drugs

Initially, responding was stabilized under the flashing-light condition. Five experimental manipulations were accomplished in the following order: D-amphetamine sulfate (0.06–0.50 mg/kg, Sigma, St. Louis, MO), caloric prefeeding, dexfenfluramine hydrochloride (0.12–1.0 mg/kg, Sigma), acute food deprivation, and diazepam (DZP; 0.25–2.0 mg/kg, courtesy of Hoffman LaRoche, Nutley, NJ). Drug doses are expressed as total weight of the salt or base. Drugs were given intramuscularly (im) in a thigh muscle (location varying among sessions) on Tuesday and Friday of each week at 0800 h prior to an extinction session, with placebo injections given occasionally on other days of the week. A complete dose-response function for each drug was determined in 2 to 3 weeks. Doses were administered only when responding on the two previous days was stable. Dose order was systematically varied within and between baboons such that all possible dosing orders were tested for each drug.

Responding was then stabilized over a 6-week period under the 1-s time-out condition. Five experimental manipulations were then accomplished in the following order: DZP (0.25–2.0 mg/kg), caloric prefeeding, dexfenfluramine hydrochloride (0.12–1.0 mg/kg), acute food deprivation, and D-amphetamine sulfate (0.06–0.50 mg/kg).

The effects of a single day's deprivation, equivalent to 75% of total daily intake of the three previous days, was determined once. Intake on a Sunday, Monday, and Tuesday was used to determine the maximal number of pellets available on Wednesday, and responding on Thursday was used to measure the effects of acute deprivation. On Wednesdays, as soon as baboons consumed the allowable number of food pellets for that day, all stimulus lights were extinguished. The effects of caloric prefeeding were also determined. At 0800 h, the baboons were provided a meal of highly preferred foods, not normally available. 'Free' meals with a caloric content equivalent to 75% of the mean caloric intake of the first taking component of the four previous days were given on Thursday. This amount corresponds to 25–30% of the mean caloric intake for an entire 24-h period. Free meals consisted of bananas (90 kcal/15 cm banana) and plain M&Ms (4.3 kcal/g, Mars, Hackettstown, NJ).

2.5. Data analysis

The total number of reinforcers earned during seeking and taking components for each drug were graphed separately, and the data points for each drug dose were considered significantly different from the placebo if the data point fell outside the 95% confidence interval for the mean of the placebo condition. The latency to the first pellet delivery of the first taking component (including the time required to complete the first seeking component), the running rate, and the 1/4 life of responding during the first seeking and taking components of each session were calculated. The quarter life is the amount of time (expressed as a proportion) that it takes for the first quarter of the responses to occur (Gollub, 1964). The greater the quarter life, the greater the responding later in the interval. Data for each drug were summarized using two-factor repeated-measures analyses of variance (ANOVA): the first factor was drug condition (placebo vs. active; there was one placebo session for each active dose session) and the second factor was dose (four doses).

Because of the large difference in the number of seeking reinforcers earned under placebo conditions for both stimulus conditions, the seeking data were not statistically compared between stimulus conditions. The number of taking reinforcers earned under placebo conditions for both stimulus conditions were similar such that direct comparisons between stimulus conditions were calculated using separate ANOVAs, with stimulus condition as the first factor, drug condition as the second factor, and dose as the third factor. These analyses were accomplished only to determine if there was a significant interaction between stimulus condition and drug condition.

Data for the deprivation manipulation were analyzed using single-factor repeated-measures ANOVAs: day of condition (base 1, base 2, base 3, day of deprivation, and day after deprivation). There was one planned comparison: data obtained on the day after deprivation were compared with the data obtained on the three baseline days. Data for the prefeeding manipulation were analyzed using single-factor repeated-measures ANOVAs: day of condition (base 1, base 2, base 3, and prefeeding day). There was one planned comparison: data obtained on the prefeeding day were compared with the data obtained on the three baseline days. Data were analyzed separately for the two stimulus conditions, and were considered significantly different at $P < .05$, using Huynh-Feldt corrections.

3. Results

3.1. Pharmacological manipulations

Under baseline conditions, when the stimuli paired with food were flashing lights, baboons earned about 50 reinforcers during seeking components (i.e., baboons responded

about 500 times) and earned about 425 reinforcers during taking components (i.e., baboons responded about 4250 times). Under baseline conditions, when the stimulus paired with food was a 1-s time out, baboons earned about 130 reinforcers during seeking components (i.e., baboons responded about 1300 times) and earned about 450 reinforcers during taking components (i.e., baboons responded about 4500 times). Thus, the baboons earned about twice as many seeking reinforcers under the 1-s time-out condition than under the flashing-light condition, but they earned about the same number of taking reinforcers under both conditions.

Fig. 1 compares the effects of the pharmacological manipulations on the daily total number of seeking reinforcers earned under both stimulus conditions. All doses of DFEN (top panels) produced similar significant decreases in the number of seeking reinforcers earned under both stimulus conditions. The effects of AMPH (middle panels) contrasted with the effects of DFEN. AMPH did not affect the daily total number of seeking reinforcers earned under the 1-s time-out condition, but nearly all doses of AMPH significantly increased the daily total number of seeking reinforcers earned under the flashing-light condition. All doses of DZP (bottom panels) produced similar significant increases in the number of seeking reinforcers earned under both stimulus conditions, but the magnitude of the effect was slightly larger under the 1-s time-out condition (70 vs. 35).

Fig. 2 compares the effects of the pharmacological manipulations on the daily total number of taking reinforcers earned under both stimulus conditions. DFEN (top panels) produced dose-dependent significant decreases in the number of taking reinforcers earned under both stimulus conditions. The effects of AMPH on the daily total number

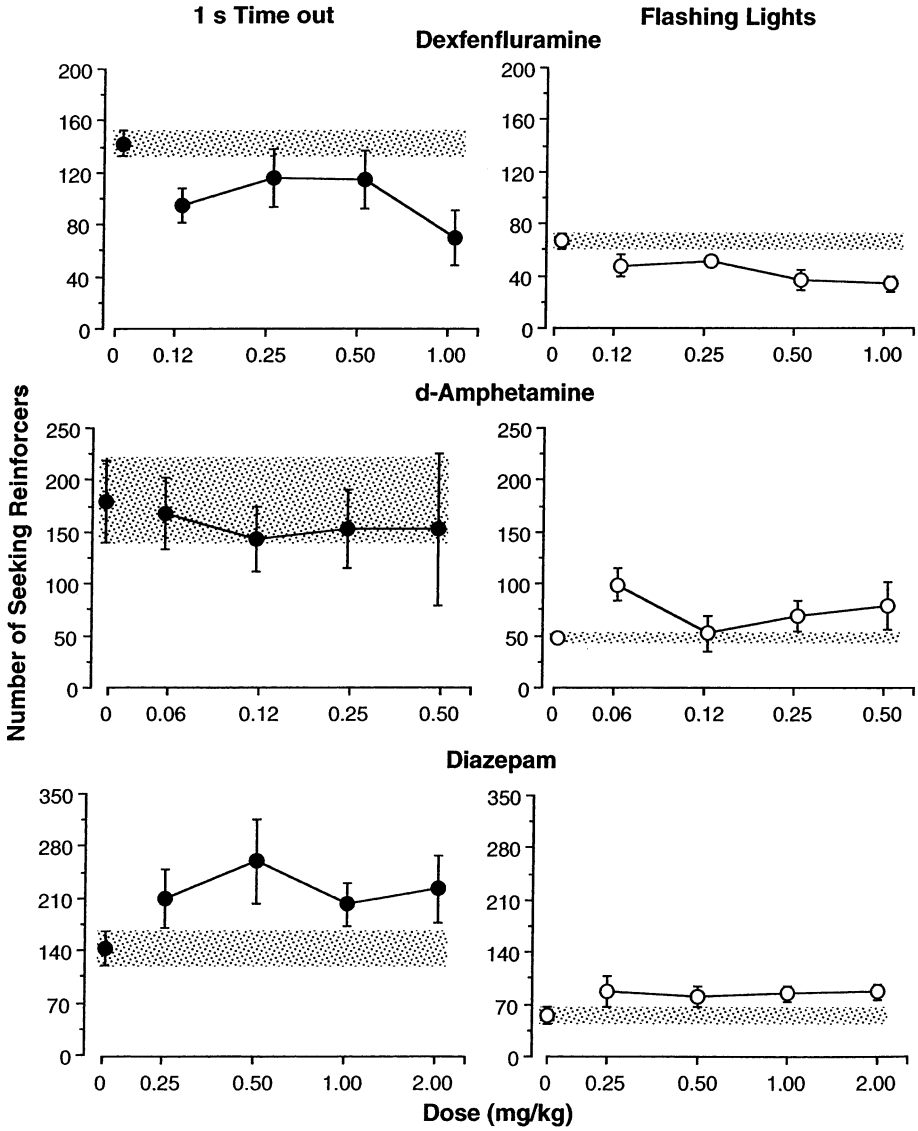

Fig. 1. Mean total daily number of seeking reinforcers as a function of drug, dose, and stimulus condition. The stippled area represents the 95% confidence interval for the number of stimulus presentations delivered during seeking components under placebo conditions. Error bars on the active drug doses represent ± 1 S.E.M.

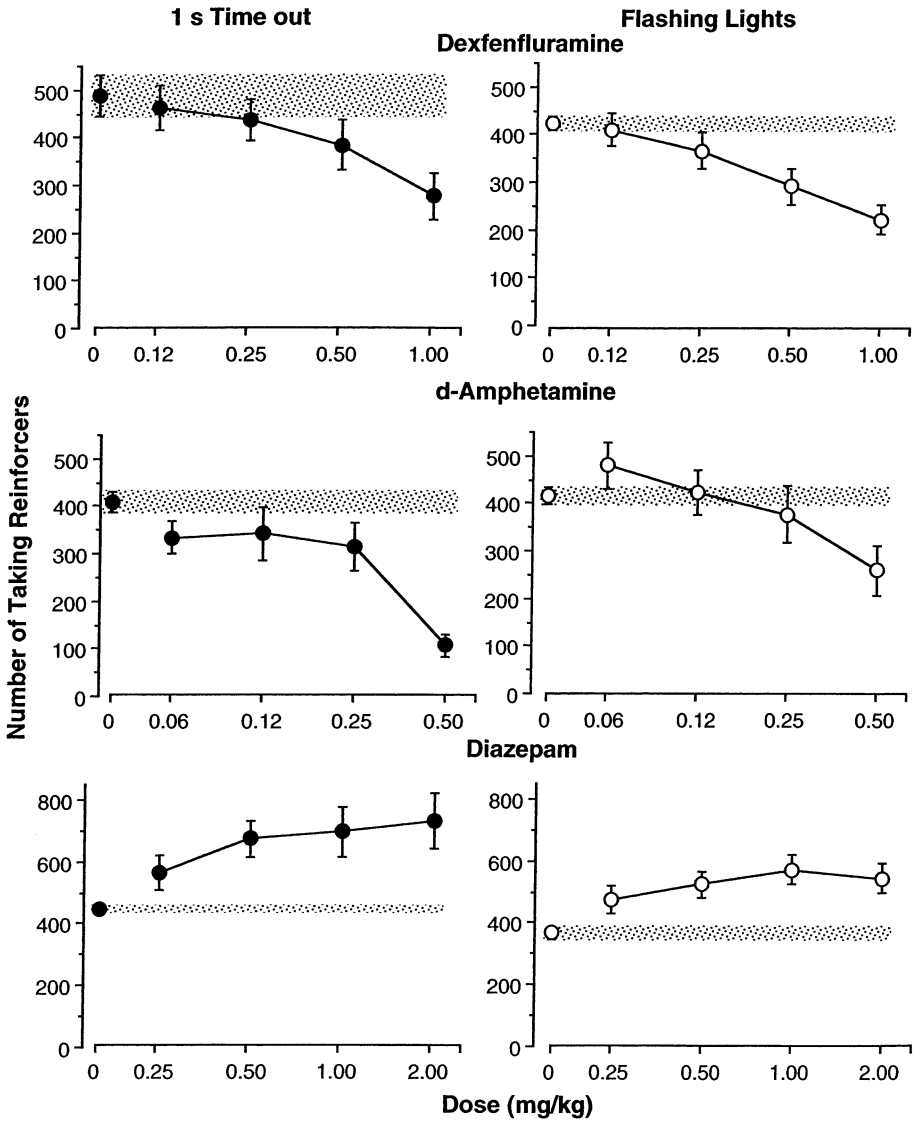

Fig. 2. Mean total daily number of taking reinforcers as a function of drug, dose, and stimulus condition. The stippled area represents the 95% confidence interval for the number of stimulus presentations delivered during taking components under placebo conditions. Error bars on the active drug doses represent ± 1 S.E.M.

of taking reinforcers varied as a function of stimulus condition. The three smaller doses of AMPH significantly decreased the daily total number of taking reinforcers earned under the 1-s time-out condition by about 50, while the largest dose significantly decreased the daily total number of taking reinforcers earned under the 1-s time-out condition by about 300. When the stimuli paired with food were flashing lights, the smallest AMPH dose significantly increased the daily total number of taking reinforcers earned by about 50. The intermediate AMPH doses had minimal effects on the daily total number of taking reinforcers earned under the flashing-light condition, while the largest AMPH dose significantly decreased the daily total number of taking reinforcers earned by about 175. As observed for seeking reinforcers, the magnitude of the effects of DZP varied between the stimulus conditions: DZP significantly increased taking reinforcers by about 300 under the 1-s time-out condition, and by about 200 taking reinforcers under the flashing-light condition. There was a significant stimulus condition by dose interaction only for AMPH: AMPH produced greater decreases in taking reinforcers under the 1-s time-out condition than under the flashing-light condition.

Under both stimulus conditions, the baboons began the first taking component of the session about 120 min after the start of the session. The largest DFEN dose significantly increased latency to about 200 min under both stimulus conditions, the largest AMPH dose significantly increased latency to about 350 min under both stimulus conditions, while all the DZP doses significantly decreased latency to about 45 min under both stimulus conditions. Mean response rate during the first seeking component of the day

was about 0.5 r/s under both stimulus conditions, while the mean response rate during the first taking component of the day was about 1.3 r/s under both stimulus conditions. Neither DFEN nor AMPH altered the running response rates. All doses of DZP significantly increased the mean response rate during the first seeking component of the day under the 1-s time-out condition by about 100%, without affecting any other response rate measure. The mean quarter life during the first seeking component of the day was about 0.38, while the mean quarter life during the first taking component of the day was about 0.26 under both stimulus conditions. Neither DFEN nor AMPH altered the quarter lives. All doses of DZP significantly increased the quarter life of the first seeking component and significantly decreased the quarter life of the first taking component by about 20%. Thus, the measures of response topography were (1) similar between the two stimulus conditions; (2) not affected by the anorectic drugs; and (3) slightly altered by DZP.

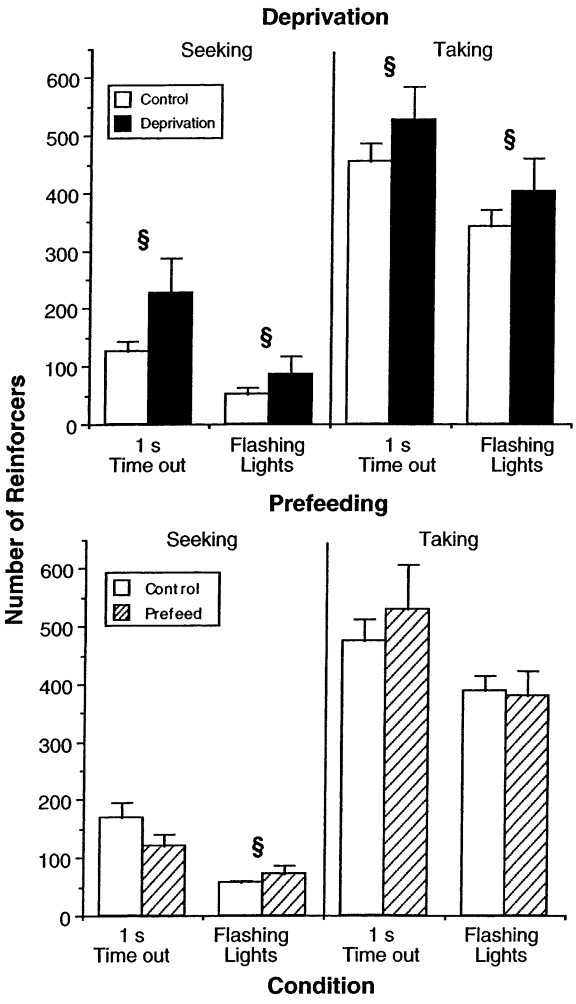

Fig. 3. Mean total daily number of seeking and taking reinforcers as a function of acute caloric deprivation and caloric prefeeding. A § indicates that the experimental condition differed significantly from the placebo control condition ($P < .05$).

3.2. Dietary manipulations

Fig. 3 compares the effects of the dietary manipulations on the daily total number of seeking and taking reinforcers earned under both stimulus conditions. Acute caloric deprivation significantly increased the daily total number of seeking reinforcers earned under both stimulus conditions, with the increase being about twice as large under the 1-s time-out condition. Acute caloric deprivation also significantly increased the daily total number of taking reinforcers earned under both stimulus conditions. Acute caloric deprivation significantly decreased the latency to the first taking component under the 1-s time-out condition (33 ± 1 vs. 96 ± 9 min) and under the flashing-light condition (44 ± 5 vs. 122 ± 14 min). As observed with DZP, acute caloric deprivation significantly increased the mean response rate during the first seeking component of the day (0.9 ± 0.2 vs. 0.6 ± 0.2 r/s) under the 1-s time-out condition, without affecting any other response rate measure. Finally, as also observed with DZP, acute caloric deprivation significantly increased the quarter life of the first seeking component (0.57 vs. 0.34).

Caloric prefeeding significantly increased the total daily number of seeking reinforcers only under the flashing-light condition. Caloric prefeeding also significantly increased the latency to the first taking component under the flashing-light condition (133 ± 12 vs. 110 ± 7 min). Caloric prefeeding had no other significant effects.

4. Discussion

The results of the present study clearly indicate that the effects of AMPH and caloric prefeeding on food seeking are dependent upon the type of stimuli paired with primary reinforcement, while the effects of DFEN, DZP, and acute caloric deprivation on food seeking are not influenced by the type of stimuli paired with primary reinforcement.

DFEN decreased the number of seeking and taking reinforcers under both stimulus conditions. The failure of the type of paired stimuli to alter the effects of DFEN suggests that the effects of DFEN are not related to a decrease in the reinforcing effects or incentive value of the paired stimuli, but are due to a decrease in motivation. Studies assessing the reinforcing effects of stimuli paired with primary reinforcement commonly use a ‘new response procedure’ (Sutton and Beninger, 1999). In this procedure, rodents are trained to associate stimulus cues with primary reinforcement; then, the rodents are given the opportunity to make an operant response to receive only the paired cues. An inactive control lever that has no consequences is also present. Under these circumstances, DFEN decreases responding on the active lever without affecting responding on the control lever (Fletcher, 1995, 1996). Because drugs that increase 5-HT are effective anorectic medications (Chaki and Nakazato, 2001; Hensrud, 2000), it is important

to note that the effects of drugs that increase 5-HT in this paradigm are not limited to decreasing the reinforcing efficacy of stimuli paired with food. Similar decreases have been observed in responding reinforced by stimuli that had been paired with water (Fletcher et al., 2002) and ethanol (Wilson et al., 2000). Combining across studies, DFEN appears to decrease motivation for a range of reinforcers; an effect that is not modulated by the type of stimuli paired with reinforcement.

DZP increased the number of seeking and taking reinforcers and, as with DFEN, this occurred under both stimulus conditions. The failure of the type of paired stimuli to alter the effects of DZP suggests that the effects of DZP are due to an increase in motivation. Because DZP is an efficacious appetite stimulant in nonhuman primates (Foltin, 1993; Foltin et al., 1989), it is most likely that these effects are due to an increase in motivation to eat. An increase or decrease in the motivation to eat should, in theory, correspondingly alter the incentive value of stimuli paired with food (Bindra, 1978; Toates, 1981); that is, an increase in motivation to eat to would increase the incentive salience of the stimuli. Because the hypothesized decrease in motivation following DFEN and the hypothesized increase in motivation following DZP were not manifested differently as a function of stimulus conditions, it seems unlikely that these manipulations specifically altered the conditioned reinforcing effects or the incentive value of the stimuli. Thus, DZP appears to increase motivation independent of stimulus conditions.

As mentioned above, the new response procedure used in rodents tests the specificity of a drug effect by comparing responding that leads to the delivery of the conditioned reinforcer to responding that has no consequences: if a dose or drug affects both types of responses, then the effect is characterized as nonspecific. This elegant procedure, however, does not take into account possible changes in motivation for the primary reinforcer, effects that would also be specific to responding that leads to the delivery of the conditioned reinforcer. It would be of interest to examine the effects of motivational manipulations on responding reinforced by paired stimuli using a new response procedure.

In contrast to the effects of DFEN and DZP, the effects of AMPH were modulated by the stimulus conditions. AMPH increased the number of seeking reinforcers under the flashing-light condition, but not under the 1-s time-out condition. AMPH, however, decreased the number of taking reinforcers under both stimulus conditions. These findings suggest that AMPH increases the conditioned reinforcing effects or the incentive value of the stimuli, even though it decreases the number of taking reinforcers. These results confirm previous data obtained using laboratory rodents (e.g., Fletcher, 1995, 1996; Wyvell and Berridge, 2000), and support the hypothesis that increases in DA increase the conditioned reinforcing effects or the incentive value of the stimuli (Robinson and Berridge, 1993). The AMPH dose-response function for taking reinforcers under the flashing-light condition was shifted to the right of the AMPH dose-response function for taking reinforcers under the 1-s time-out condition. In fact, the lowest AMPH dose increased the number of taking reinforcers under the flashing-light condition, suggesting that the positive effect of AMPH on the reinforcing effects or incentive value of stimuli offsets the anorectic actions of AMPH. An increase by low AMPH doses of the incentive value of paired stimuli may account for the occasional reports of low doses of AMPH increasing food intake (e.g., Foltin and Schuster, 1983).

An interesting pattern emerges when the dose-response functions for seeking and taking behavior are compared with each other. None of the three pharmacological manipulations produced dose-dependent effects on seeking behavior, while all three pharmacological manipulations produced dose-dependent effects on taking behavior. A wider range of doses needs to be determined to better describe the shape of seeking behavior dose-response functions. The results further confirm that seeking and taking behavior can be pharmacologically differentiated and indicate that more research is needed to understand the biological mechanism mediating taking behavior.

Two naturalistic feeding manipulations were included to provide comparison data for the pharmacological manipulations: acute caloric deprivation and caloric prefeeding. The effects of caloric deprivation mirrored that of DZP: caloric deprivation increased the number of seeking and taking reinforcers under both stimulus conditions. The similar effects of DZP and deprivation support the argument that the effects of DZP in this paradigm reflect an increase in motivation to eat. Of course, an increase in motivation should increase the incentive value of stimuli; but because the effects of deprivation did not vary as a function of stimulus condition, a change in motivation provides the most parsimonious account of the data. Alternatively, it is likely that acute caloric deprivation also functions as a stressor. Much data obtained using laboratory animal models of drug relapse indicate that stress reliably increases responding that had been previously reinforced by either the drug itself or stimuli paired with drug; that is, stress can increase incentive motivation (Shaham et al., 2003). In this case, the increase in incentive motivation was not modulated by the type of stimuli paired with reinforcement.

The effects of caloric prefeeding on responding during seeking components mirrored that of AMPH: prefeeding increased the number of seeking reinforcers under the flashing-light condition, but not under the 1-s time-out condition. Caloric prefeeding was chosen to test because, like anorectic drugs, and as observed here, caloric prefeeding with preferred foods decreases food intake in nonhuman primates (Foltin and Fischman, 1990). Because the preferred foods that were used for prefeeding are effective reinforcers, and food reinforcers have been shown to increase DA in rats (Bassareo and Di Chiara, 1999) and nonhuman primates (Schultz, 1992), it is tempting to speculate that caloric prefeeding increased food seeking because of an effect on DA.

The preload provided a small part of each baboon's total daily intake (approximately 25%), and being comprised of preferred foods may have caused an increase in motivation to work for food similar to the human phenomena known as the 'appetizer effect' (Yeomans, 1996). The effect of prefeeding was modulated by the stimulus condition, indicating that a nonspecific increase in motivation cannot account for the results. The present results suggest that prefeeding with a nonpreferred food or the standard food pellets would not increase food-seeking behavior. Unfortunately, when presented with such food, baboons will not eat them avidly, making it impossible to use nonpreferred food or the standard food pellets in a prefeeding condition.

One difficulty with the current procedures is that the pattern of responding varied between the two stimulus conditions. Although the number of taking reinforcers was similar between conditions, baboons responded about twice as much during seeking components under the 1-s time-out condition compared with the flashing-light condition. This increase was most likely due to the fact that the time out after stimulus presentations was 30 s under the flashing-light condition, which provided the baboons with less time to respond. In addition, either the longer time out or the presentation of light flashes may have contributed to longer pauses between bursts of responding under the flashing-light condition. It has been repeatedly demonstrated that AMPH increases responding that occurs at a low rate and decreases responding that occurs at a high rate, that is, 'rate dependency' (Kelleher and Morse, 1968). Although there were more stimulus deliveries under the 1-s time-out condition, the actual rate of responding did not differ between the two stimulus conditions. Thus, if rate-dependent effects of AMPH would had been observed, they would have been similar under both stimulus conditions due to the similar rates of responding. The increase in seeking behavior following AMPH is also not likely to be due to a nonspecific increase in responding, as the same effect was observed for caloric prefeeding.

In summary, the effects of DFEN, DZP, and acute caloric deprivation on food seeking and food taking were independent of the type of stimuli that was paired with food and presented during the second-order seeking component. In contrast, the effects of AMPH and caloric prefeeding on food seeking and taking were dependent upon the type of stimuli that was paired with food and presented during the second-order seeking component. This pattern of results suggests that the appetitive effects of DFEN, DZP, and acute caloric deprivation are related to changes in motivation, while the effects of AMPH and caloric prefeeding are modulated, in part, by changes in the conditioned reinforcing effects or incentive salience of the stimuli paired with food.

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References

Bassareo V, Di Chiara G. Differential responsiveness of dopamine transmission to food-stimuli in nucleus accumbens shell/core compartments. Neuroscience 1999;89:637–41.

Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Brain Res Rev 1998;28:309–69.

Bindra D. How adaptive behavior is produced: a perceptual-motivational alternative to response-reinforcement. Behav Brain Sci 1978;1:41–91.

Chaki S, Nakazato A. Recent advances in feeding suppressing agents: potential therapeutic strategy for the treatment of obesity. Expert Opin Ther Pat 2001;11:1677–92.

Collier GH. Life in a closed economy: the ecology of learning and motivation. New York: Wiley; 1983.

Collier G, Hirsch E, Kanarek R. The operant revisited. Englewood Cliffs (NJ): Prentice-Hall; 1977.

Fletcher PJ. Effects of D-fenfluramine and metergoline on responding for conditioned reward and the response potentiating effect of nucleus accumbens D-amphetamine. Psychopharmacology 1995;118:155–63.

Fletcher PJ. Injection of 5-HT into the nucleus accumbens reduces the effects of D-amphetamine on responding for conditioned reward. Psychopharmacology 1996;126:62–9.

Fletcher PJ, Korth KM, Robinson SR, Baker GB. Multiple 5-HT receptors are involved in the effects of acute MDMA treatment: studies on locomotor activity and responding for conditioned reinforcement. Psychopharmacology 2002;162:282–91.

Foltin RW. Effects of pharmacological manipulations on "demand" for food by baboons. Behav Pharmacol 1993;4:586–96.

Foltin RW. Effects of amphetamine, dexfenfluramine, diazepam, and other pharmacological and dietary manipulations on food "seeking" and "taking" behavior in non-human primates. Psychopharmacology 2001;158:28–38.

Foltin RW, Fischman MW. The effects of varying procurement costs on food intake in baboons. Physiol Behav 1988;43:493–9.

Foltin RW, Fischman MW. Effects of caloric manipulations on food intake in baboons. Appetite 1990;15:135–49.

Foltin RW, Schuster CR. Interaction between the effects of intragastric meals and drugs on feeding in rhesus monkeys. J Pharmacol Exp Ther 1983;226:405–10.

Foltin RW, Fischman MW, Byrne MF. Food intake in baboons: effects of diazepam. Psychopharmacology 1989;97:443–7.

Gollub J. The relations among measures of performance on fixed interval schedules. J Exp Anal Behav 1964;7:337–43.

Hensrud DD. Pharmacotherapy for obesity. Med Clin North Am 2000;84:463–76.

Highfield DA, Mead AN, Grimm JW, Rocha BA, Shaham Y. Reinstatement of cocaine seeking in 129X1/SvJ mice: effects of cocaine priming, cocaine cues and food deprivation. Psychopharmacology 2002;161:417–24.

Kelleher RT. Conditioned reinforcement in second-order schedules. J Exp Anal Behav 1966;9:475–85.

Kelleher RT, Morse WH. Determinants of the specificity of behavioral effects of drugs. Ergeb Physiol 1968;60:1–56.

Levison PK, Gerstein DR, Maloff DR, editors. Commonalities in substance abuse and habitual behavior. Lexington (MA): Lexington Books; 1983.

Mackintosh NJ. The psychology of animal learning. New York: Academic Press; 1974. United States Edition.

Mule SJ, editor. Behavior in excess. New York: The Free Press; 1981.

Owen J. Feeding strategy. Chicago (IL): The University of Chicago Press; 1980.

Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Rev 1993;18:247–91.

Schultz W. Activity of dopamine neurons in the behaving primate. Semin Neurosci 1992;4:129–38.

Shaham Y, Shalev U, Lu L, deWit H, Stewart J. The reinstatement model of drug relapse: history, methodology and major findings. Psychopharmacology 2003;168:3–20.

Sutton MA, Beninger RJ. Psychopharmacology of conditioned reward: evidence for a rewarding signal at D1-like dopamine receptors. Psychopharmacology 1999;144:95–110.

Toates FM. The control of ingestive behaviour by internal and external stimuli—A theoretical review. Appetite 1981;2:35–50.

Wilson AW, Costall B, Neill JC. Manipulation of operant responding for an ethanol-paired conditioned stimulus in the rat by pharmacological alteration of the serotonergic system. J Psychopharmacol 2000;14:340–6.

Woods JH, Winger GD. Observing responses maintained by stimuli associated with cocaine or remifentanil reinforcement in rhesus monkeys. Psychopharmacology 2002;163:345–51.

Wyvell CL, Berridge KC. Intra-accumbens amphetamine increases the conditioned incentive salience of sucrose reward: enhancement of reward ''wanting'' without enhanced ''liking'' or response reinforcement. J Neurosci 2000;20:8122–30.

Yeomans MR. Palatability and the micro-structure of feeding in humans: the appetizer effect. Appetite 1996;27:119–33.