Pharmacology Biochemistry and Behavior, Vol. 62, No. 3, pp. 457–464, 1999

0091-3057/99 $–see front matter

PII S0091-3057(98)00217-2

The Effects of *d*-Amphetamine on Intake of Food and a Sweet Fluid Containing Cocaine

RICHARD W. FOLTIN AND SUZETTE M. EVANS

Division on Substance Abuse, New York State Psychiatric Institute and Department of Psychiatry, College of Physicians and Surgeons of Columbia University, 1051 Riverside Dr., Unit 120, New York, NY 10032

Received 20 March 1998; Revised 13 July 1998; Accepted 12 August 1998

FOLTIN, R. W. AND S. M. EVANS. *The effects of* d-*amphetamine on intake of food and a sweet fluid containing cocaine.* PHARMACOL BIOCHEM BEHAV **62**(3) 457–464, 1999.—Using a laboratory animal procedure designed to measure two aspects of reinforcement (self-administration and location preference), five adult rhesus monkeys each lived in three chambers: oral cocaine self-administration (0.26 mg/kg/delivery cocaine hydrochloride in a sweet fluid) was specific to one end chamber, food self-administration was specific to the other end chamber, and no food cues or fluid cues were available in the middle chamber. Throughout the 10-h experimental day monkeys experienced multiple food, cocaine, and choice (food vs. sweet cocaine fluid), sessions. Oral *d*-amphetamine (AMPH; 0.5–1.5 mg/kg) or placebo was administered before the sessions to determine if this anorectic drug would differentially alter food and sweet cocaine fluid self-administration. Further, the effects of AMPH on the length of time a monkey spent in each chamber, when the stimulus cues indicating commodity availability were not present (location preference) were determined. AMPH produced dose-dependent decreases in both food and cocaine self-administration without affecting choice behavior. AMPH also increased the length of time monkeys spent in the food chamber, even when no stimuli indicating food availability were present. These results indicate that the relationship between self-administration and location preference measures of reinforcement is not completely concordant. The current procedure may prove useful in studying these two measures of reinforcement. © 1999 Elsevier Science Inc.

Food intake Cocaine *d*-Amphetamine Self-administration Location preference Place preference Reinforcement Rhesus monkey Time allocation Choice

A previous study from this laboratory (6) examined the effects of amphetamine (AMPH) on behavior related to food and fluid self-administration by rhesus monkeys. The protocol used in that study combined aspects of both self-administration and conditioned place preference (CPP) procedures, which are commonly used to estimate reinforcement. Self-administration procedures measure operant responding for contingent drug delivery and define reinforcement based on rates of drug intake relative to rates of saline or vehicle intake. CPP procedures repeatedly pair a drug with a specific environment and vehicle with a different environment during a training phase, and define reinforcement based on the length of time spent in the environment paired with drug compared to the environment paired with placebo. Both self-administration procedures (19) and CPP (3,4,12) provide data about mechanisms of drug abuse.

Self-administration and preference measures of reinforcement were obtained in the previous study (6) by having rhesus monkey live in three chambers with fluid self-administration specific to one end chamber and food self-administration specific to the other end chamber. Operant responding reinforced by each commodity provided a self-administration measure of reinforcement. The length of time monkeys spent in a chamber when neither commodity nor stimuli paired with each commodity were available (other than the physical location of the three different chambers) provided a location preference measure of reinforcement, AMPH decreased both food and fluid self-administration, but responding for fluid was reduced to a greater extent than responding for food. However, AMPH increased the length of time monkeys spent in the food chamber, even when no stimulus lights indicating food availability were illuminated. The relationship between self-administration and location preference measures of reinforcement was not completely concordant.

Although the location-preference measure, based on the length of time a monkey spent in a chamber when the com-

Requests for reprints should be addressed to Richard W. Foltin, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, Unit 120, New York, NY 10032.

modity was not available is procedurally similar to the testing phase of CPP paradigms, there are several important differences. In place-preference training, drug is usually administered noncontingently to animals confined to the test environment with no access to alternative commodities in the alternate chamber, and subjects do not live in the test chambers (3,22). An equivalent place-preference procedure would pair the animal's only source of food with one location and drug with another. In CPP procedures, the conditioning and testing trials are relatively short, whereas in this procedure the animals have the ability to move from chamber to chamber throughout the day. And, finally, estimates of reinforcement are obtained in CPP procedures in the absence of drug, while in this procedure, location preference is measured while animals may be experiencing drug effects.

The increase in time spent in the food chamber and decrease in food intake following AMPH administration in our previous study (6) may have been related to the alternative fluid commodity, rather than to discordant effects of AMPH on these two measures of reinforcement. This appears to have been the case, at least in part, because the increase in the length of time spent in the food chamber was predicted by the decrease in the number of fluid deliveries, not the number of food deliveries, i.e., monkeys may have spent more time in the food chamber to avoid spending time in the fluid chamber. The purpose of this study was to test the hypothesis that the increase in time spent in the food chamber following AMPH pretreatment in our previous study was related to the use of a sweet fluid alternative, rather than an effect of AMPH on food-related behavior per se. This possibility was evaluated by examining the effects of AMPH on behavior related to food when the alternative was a sweet cocaine fluid. Cocaine was chosen, because in a previous study with these monkeys (9) oral cocaine self-administration engendered a significantly greater location preference for the fluid chamber than vehicle.

METHOD

Animals and Apparatus

Five adult male rhesus monkeys (*Macaca mulatta*), weighing between 5.4 and 7.3 kg, lived under the housing conditions described below. In addition to food pellets delivered under the operant schedule, each monkey received chewable vitamins and a piece of fruit daily, and occasional treats. Body weights, determined weekly, remained stable throughout the study. Monkeys were housed in customized, squeeze-capable, rack-mounted, nonhuman primate cages (Hazleton Systems, Inc., Aberdeen, MD). Each monkey had access to three identically sized chambers (61.5 cm wide $\times$ 66.5 cm deep $\times$ 88 cm high) connected to one another by 40 cm $\times$ 40 cm openings. For three of the monkeys, sweet cocaine fluid self-administration occurred in the left end chamber and food self-administration occurred in the right end chamber. These locations were reversed for the other two monkeys. No self-administered commodities were available in the middle chamber. Water was freely available from spouts located on the back wall of all three chambers. All activity was monitored (see below), and schedule contingencies were controlled by customized software (Eureka Software, Cary, NC) running on two Macintosh 610 computers (Cupertino, CA) located in an adjacent area. The room lights were illuminated from 0800 to 2000 h.

Stimulus response panels were located on the front wall of each of the chambers. Six session lights (CM 1820, 24 v, Chicago Miniature, Buffalo Grove, IL) with white lenses were evenly spaced around the outside edges of each panel. Two Lindsley levers (BRS-LVE, Beltsville, MD), with a light over each, were mounted at the bottom of each panel. The food-response panel also had a food hopper, a pair of green lights over the hopper, and a pellet dispenser (BRS-LVE model PDC-005, Beltsville, MD) mounted on the outside. The fluid-response panel had a spout for fluid delivery and a red light over and beneath the spout, a peristaltic pump (7543-06 with pump head 7016; flow rate of 10 ml/min; Cole Parmer Co., Chicago, IL), and a fluid source mounted on the outside. An infrared heat and motion detector (Motion Sensor, Radio Shack, Ft. Worth, TX), which was activated when the monkey was in that chamber, was attached to each of the end chambers. Location of each monkey was recorded every 30 s.

Operant Schedule

Responding maintained by food pellets or a sweet fluid containing cocaine was reinforced according to a two-component chained schedule of reinforcement with responding during each component on a separate level (6,9). The first component, signalled by a yellow light over the left lever, was a second-order fixed-interval (FI) 10 min schedule with fixed-ratio (FR) 40 components of stimulus delivery [FI 10′ (FR 40:S)]. Thus, after every 40th response during the first component, the stimuli associated with the sweet cocaine fluid (a steady red light over and below the fluid spout) or food (two flashing green lights over the food hopper) were presented for 10 s. Responses emitted during the brief stimulus presentations were not counted. The first FR 40 completed after 10 min resulted in the lever light over the left lever being extinguished and an amber lever light over the right lever being illuminated, signalling the availability of reinforcement according to the second component of the chained schedule. The second component, which required responses on the right lever, was a FR 20 schedule with a 30-s time out (TO) after reinforcer delivery, when responding had no programmed consequences [FR 20 (TO 30″)]. Responding in the food chamber was reinforced by the delivery of a 1-g food pellet (Formula L banana-flavored, 3.7 kcal: 21.0% protein, 4.7% fat, 62.0% carbohydrate, 5.3% ash, 3.1% moisture and 3.0% fiber, Noyes, Co., Inc., Lancaster, NH). Responding in the fluid chamber was reinforced by 5 ml of fluid (two 15-s deliveries with a 5-s pause between deliveries). The fluid consisted of cocaine hydrochloride (Courtesy of The National Institute on Drug Abuse) in a 0.25 kcal/ml dilute strawberry-raspberry flavored solution [260 g glucose (3.85 kcal/g, Sigma Chemical Co., St. Louis, MO) dissolved in 4000 ml tap water with one packet of Increadiberry Kool-Aid® (Kraft General Foods, White Plains, NY)] to yield a cocaine dose of 0.26 mg/kg/delivery (9).

Procedure

Each 10-h experimental day, which began at 0900 h, consisted of six cycles of each of the five types of 20-min sessions: 1) food available, 2) sweet cocaine fluid available, 3) food or sweet cocaine fluid available in a choice trial, 4) no commodity available (session lights illuminated in the middle chamber), and 5) no illuminated session lights. The maximum number of deliveries during the consumption component of food and sweet cocaine fluid sessions was 17 and 9, respectively. The length of the food consumption component was chosen so that it would be possible for monkeys to earn all of their daily food ration during the experimental day: there was no supplemental chow ration. Fluid consumption components

were kept the same length as food consumption components so that total access time to reinforcers was the same for both reinforcers, not counting time spent in choice sessions. Because fluid took longer to deliver than a food pellet, this decreased the number of fluid deliveries that could be earned per consumption component. During choice sessions, session and lever lights in both the food and sweet cocaine fluid chambers were illuminated. The first response on either left lever terminated the schedule opportunity in the alternate chamber and initiated the FI component for the chosen commodity. Session order within each cycle was systematically varied, with the exception that a choice session could not follow a food or sweet cocaine fluid session.

Approximately twice a week, animals had test days, usually Mondays and Thursdays, assuming food and sweet cocaine fluid intake were stable on the previous days, i.e., no increasing or decreasing trends in food and fluid intake on preceding nontest days. On these test days monkeys were given an oral pretreatment of AMPH (0.5 to 1.5 mg/kg; Sigma Chemical Corp., St. Louis, MO) 30 min before the start of the daily session. The appropriate amount of AMPH stock solution (10 mg/ml concentration) was added to 40–60 ml of concentrated Kool-Aid (Tropical Punch made with 20% of the water recommended) and administered orally via vinyl tubing (which functioned like a straw) in the middle chamber. On most nontest days throughout the experiment, animals were given the concentrated Kool-Aid solution without AMPH before the daily session. Each dose of AMPH was tested twice: once under a test schedule when the day began with a food session, and once under a test schedule when the day began with a sweet cocaine fluid session.

Data Analysis

Latency to the first response, overall response rate, the number of second-order stimulus deliveries during the FI components, and the number of reinforcers earned during the FR components were summarized for food and sweet cocaine fluid sessions. The number of food choice sessions chosen each day were also summarized. Drug dose was coded as low, medium, and high in the analyses because one monkey was more sensitive to the effects of AMPH (i.e., his food and fluid intake following 1.0 mg/kg was similar to that observed following 1.5 mg/kg AMPH in the remaining monkeys), and tested with 0.5 (low), 0.75 (medium), and 1.0 (high) mg/kg AMPH. All other monkeys were tested with 0.5, 1.0, and 1.5

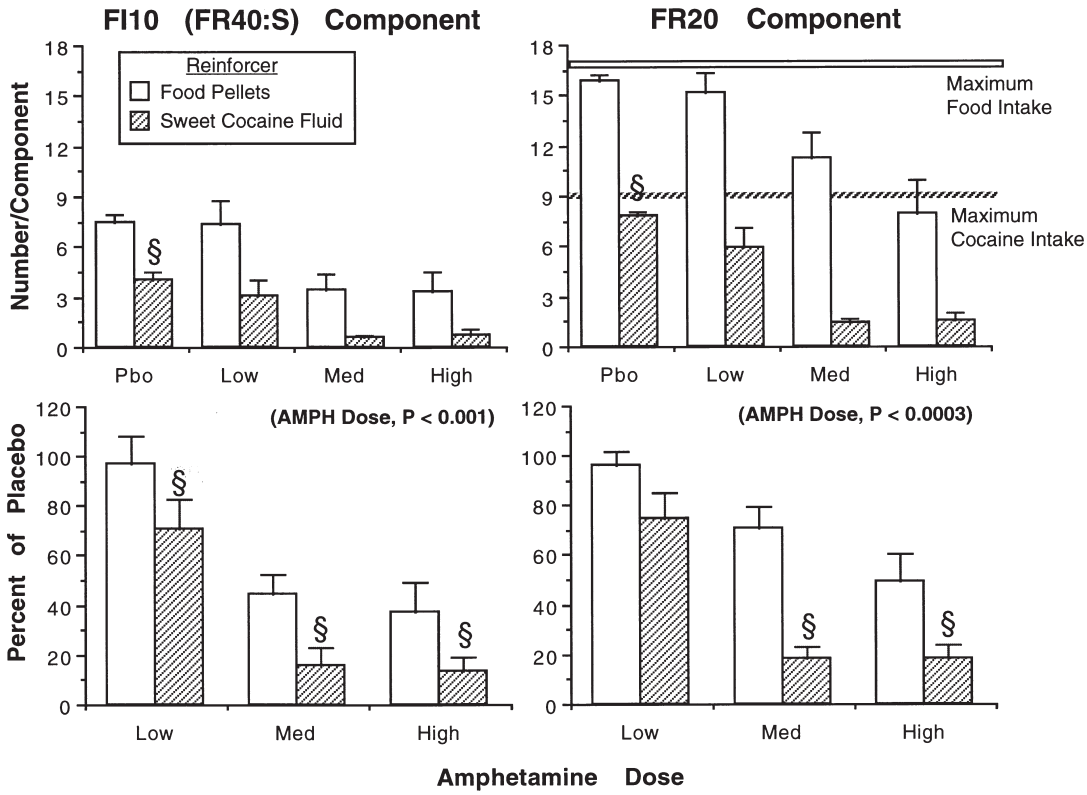

FIG. 1. Upper left panel: mean number of second-order stimulus deliveries earned during FI components of food and fluid sessions as a function of an AMPH dose condition. Upper right panel: mean number of reinforcers earned during FR components of food and fluid sessions as a function of an AMPH dose condition. The open horizontal bars represent the maximum number of food reinforcers that could be obtained, and the striped horizontal bar represents the maximum number of sweet cocaine fluid reinforcers that could be obtained. Lower panels: AMPH dose condition data from the above panels expressed as a percent of placebo baseline. Pbo = placebo; Low, Med (medium) and High refer to the doses of AMPH because one monkey did not receive the same doses as the other four monkeys. Data shown are the mean of six daily food or sweet cocaine fluid sessions. Error bars represent 1 SEM. An § indicates a significant difference between food and sweet cocaine fluid sessions under that AMPH dose condition.

mg/kg AMPH. Data collected on the day prior to each AMPH pretreatment served as baseline. The first set of analyses determined if there were significant differences between responding maintained by sweet cocaine fluid and responding maintained by food under placebo conditions. Analyses were accomplished using a three-factor repeated-measures analyses of variance (ANOVA), with reinforcer as the first factor (food, 0.26 mg/kg/delivery cocaine in a sweet fluid), AMPH dose as the second factor (placebo, low, medium, and high) and test session type as the third factor (fluid first vs. food first). Data from a single planned comparison (fluid placebo vs. food placebo) were used from this set of analyses. The analysis of the effects of AMPH were accomplished using data that were transformed to percent change of placebo baseline. These data were also analyzed using three-factor repeated-measures analyses of variance (ANOVA) with reinforcer as the first factor (food, 0.26 mg/kg/delivery cocaine in a sweet fluid), AMPH dose as the second factor (low, medium, and high) and test session type as the third factor (fluid first vs. food first). Planned comparisons between the two reinforcers at each AMPH dose were also conducted.

Using the three-chamber living arrangement, rhesus monkeys spent much time walking (or running) between all three chambers, and often sat on the squeeze bar at the side of the chambers with their tails in one chamber and their heads in another. If a monkey was in more than one chamber, of if a monkey was quite still, such as when sleeping, or otherwise "lost" to the location detector, it was classified by the automated system as being in the middle chamber. Thus, time spent in the food and fluid chambers was estimated conservatively, and the middle chamber was the default location. The length of time that monkeys spent in each end chamber when 1) the stimuli indicating food availability were illuminated, 2) the stimuli indicating fluid availability were illuminated, and 3) none of the stimulus lights signalling reinforcer availability were illuminated, were analyzed as described above.

Last, regression analyses were conducted between the mean number of food or sweet cocaine fluid deliveries during the FR components of self-administration sessions and the mean length of time spent in the food chamber when no stimulus lights were illuminated. If a significant relationship between self-administration and location preference was observed, the amount of variance accounted for by this relationship was derived from the squared multiple *r*-value. Results for all analyses were considered significant at $p < 0.05$, using Hunyh-Feldt corrections where appropriate.

RESULTS

The top panels of Fig. 1 show the mean number of second-order stimulus deliveries during FI components and reinforcers delivered during the FR components of food and fluid sessions as a function of AMPH dose condition. After placebo pretreatment monkeys earned about eight conditioned-stimulus presentations during FI components of food sessions and

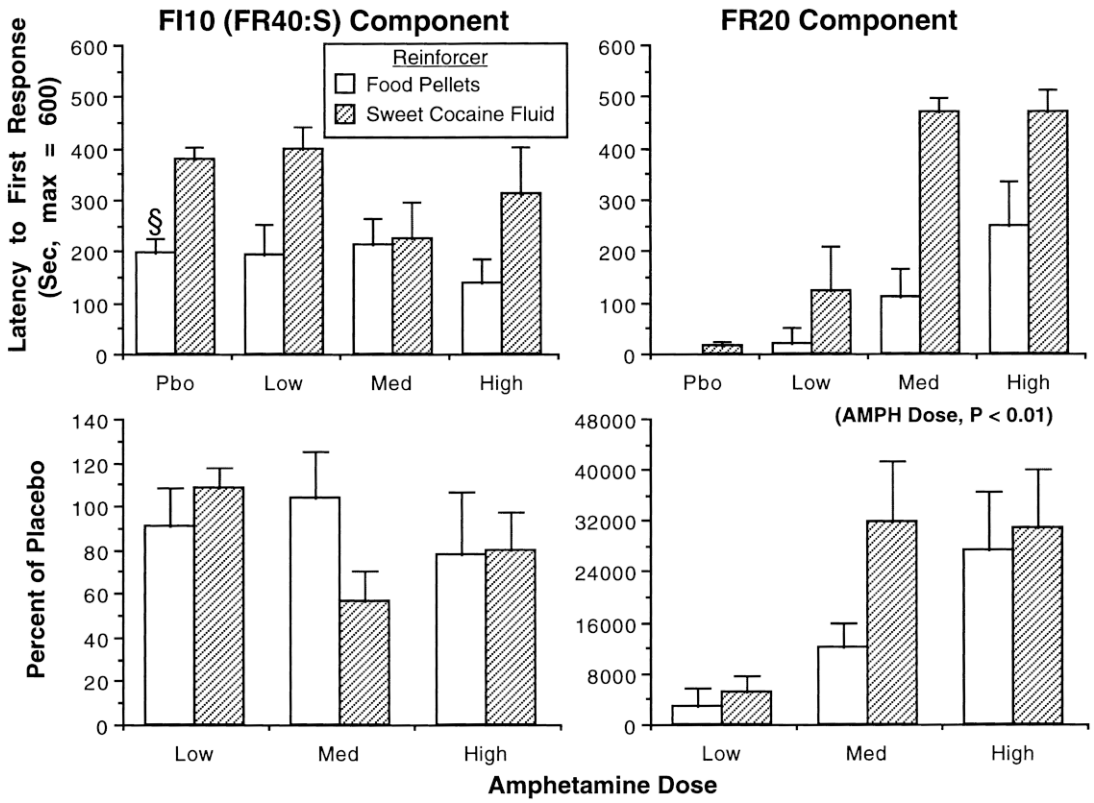

FIG. 2. Upper left panel: mean latency to the first response of FI components of food and sweet cocaine fluid sessions as a function of AMPH dose condition. Upper right panel: mean latency to the first response of FR components of food and sweet cocaine fluid sessions as a function of AMPH dose condition. Lower panels: AMPH dose condition data from the above panels expressed as a percent of placebo baseline. See Fig. 1 for details.

only about four conditioned-stimulus presentations during FI components of fluid sessions (upper left panel). After placebo pretreatment monkeys earned close to the maximum number (17) of pellet deliveries during FR components of food sessions and close to the maximum number of sweet cocaine fluid deliveries (9) during FR components of fluid sessions (upper right panel). The AMPH data shown in the top two panels of Fig. 1 are regraphed as percent change from placebo baseline in the bottom two panels of Fig. 1. AMPH produced a dose-related decrease in the number of second-order stimulus deliveries during FI components, $F(2, 8) = 17.8, p < 0.001$, and reinforcer deliveries during FR components, $F(2, 8) = 25.7, p < 0.0003$. The medium and high AMPH dose conditions decreased sweet cocaine fluid intake to a greater extent than food intake.

Monkeys chose food on 4.6 ± 0.4 (mean ± SEM; data not shown) of the six choice opportunities each day. AMPH pretreatment did not alter the number of times food was chosen over sweet cocaine fluid each day.

The top panels of Fig. 2 show the mean latency to the first response of FI and FR components of food and fluid sessions as a function of AMPH dose condition. Latency to the first response during FI components was significantly shorter during food sessions than fluid sessions under placebo conditions (upper left panel). AMPH pretreatment did not significantly affect the latency to the first response of food or fluid sessions (bottom left panel). In contrast to FI components, there was no difference in the latency to make the first response of FR components between food and fluid sessions (top right panel). AMPH pretreatment significantly increased the latency to the first response during FR components of both food and fluid sessions, $F(2, 8) = 8.4, p < 0.01$; lower right panel.

The top panels of Fig. 3 show the mean rate of responding during FI and FR components of food and fluid sessions as a function of AMPH dose condition. There was no difference between food and fluid sessions in the rate of responding during FI components (top left panel) under placebo conditions. AMPH pretreatment significantly decreased response rate during FI components of both food and fluid sessions, $F(2, 8) = 11.6, p < 0.004$; lower left panel. In contrast to FI components, monkeys responded at a greater rate during the FR component of food sessions than the FR component of fluid sessions under placebo conditions (upper right panel). AMPH pretreatment significantly decreased response rate during FR components of both food and fluid sessions, $F(2, 8) = 9.2, p < 0.02$; lower right panel, but these decreases were proportionally larger under each AMPH dose condition when responding was maintained by sweet cocaine fluid.

The top panels of Fig. 4 show the length of time monkeys spent in the food and fluid chambers when fluid stimulus lights were illuminated and when no stimulus lights were illuminated (i.e., no commodities were available) as a function of AMPH dose condition. Under placebo conditions, monkeys spent significantly more time in the fluid chamber than in the food chamber during fluid sessions (upper left panel). Although AMPH did not have a significant dose-dependent effect on location preference during fluid sessions, the medium- and high-AMPH dose conditions altered location preference

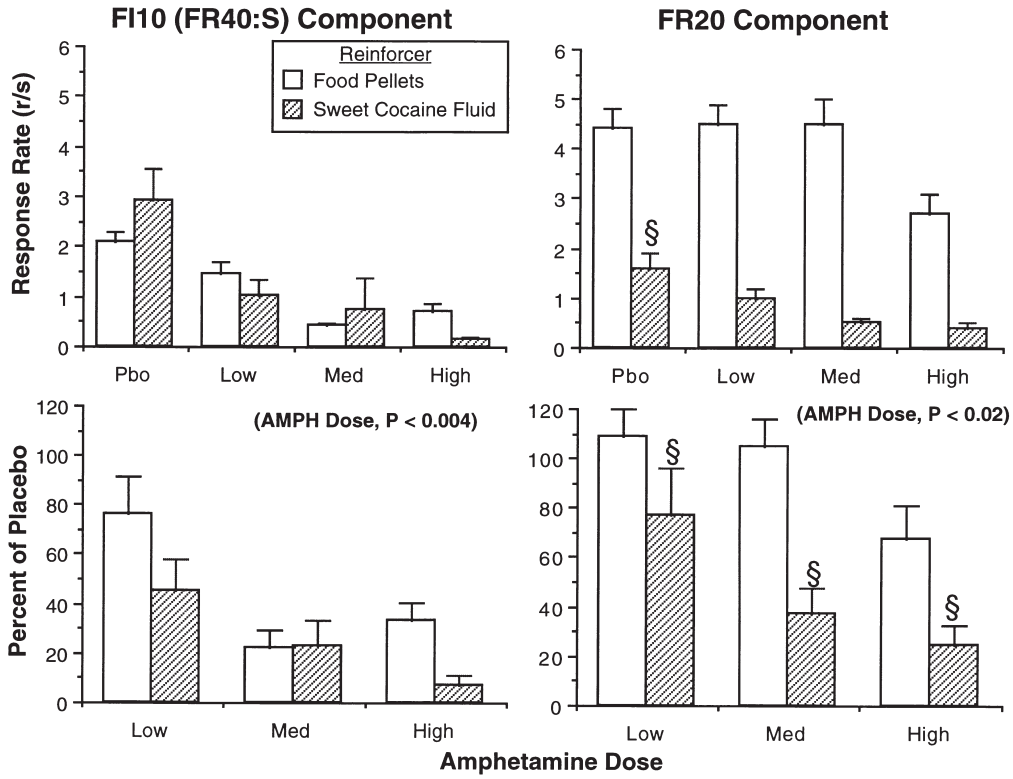

FIG. 3. Upper left panel: mean response rates during FI components of food and sweet cocaine fluid sessions as a function of AMPH dose condition. Upper right panel: mean response rates during of FR components of food and sweet cocaine fluid sessions as a function of AMPH dose condition. Lower panels: AMPH dose condition data from the above panels expressed as a percent of placebo baseline. See Fig. 1 for details.

during fluid sessions by increasing the length of time monkeys spent in the food chamber during fluid sessions (lower left panel). Under placebo conditions, monkeys spent significantly more time in the food chamber (99 ± 9 min) than in the fluid chamber (11 ± 2 min) during food sessions ($p < 0.0001$; data not shown). AMPH did not produce any significant change in the length of time monkeys spent in the food chamber during food sessions. Under placebo conditions, monkeys spent an equal amount of time in the food and fluid chambers in the absence of stimuli indicating commodity availability (upper right panel). Although AMPH did not have a significant dose-dependent effect on location preference when neither food nor fluid were available, the medium- and high-AMPH dose conditions altered location preference when neither food nor fluid were available by increasing the length of time monkeys spent in the food chamber in the absence of stimuli indicating commodity availability (lower right panel).

There was an inverse relationship between the length of time spent in the food chamber and the number of food deliveries, which accounted for 23% of the variance, $F(1, 38) = 11.3$, $p < 0.002$: as the number of food deliveries decreased, monkeys spent significantly more time in the food chamber when no stimulus lights were illuminated. There was no significant relationship between the number of sweet cocaine fluid deliveries and the length of time spent in the food chamber when no stimulus lights were illuminated: <10% of the variance in time spent in the food chamber was accounted for by the number of sweet cocaine fluid deliveries.

DISCUSSION

The purpose of this study was to determine if the effects of AMPH on food intake and time spent in the food chamber when a sweet fluid containing cocaine was also available for self-administration would vary from a previous study in which the two reinforcers were food and a sweet fruit-flavored drink (6). AMPH produced dose-dependent decreases in food and sweet cocaine fluid intake without affecting choice to experience food sessions vs. sweet cocaine fluid sessions, and produced dose-dependent increases in the length of time monkeys spent in the food chamber when neither food nor fluid were available. The discrepancy between the food self-administration results and the location-preference measure replicates the previous study (6). In contrast, AMPH did not alter choice for food pellets.

The decrease in food intake following AMPH is consistent with previous reports (5,10,11), as is the ability of AMPH to decrease cocaine self-administration (14,15). For example, in monkeys trained to self-administer food and intravenous cocaine, pretreatment with 0.56 mg/kg AMPH decreased responding for food to a greater extent than responding for cocaine, whereas 1.0 mg/kg AMPH similarly decreased responding

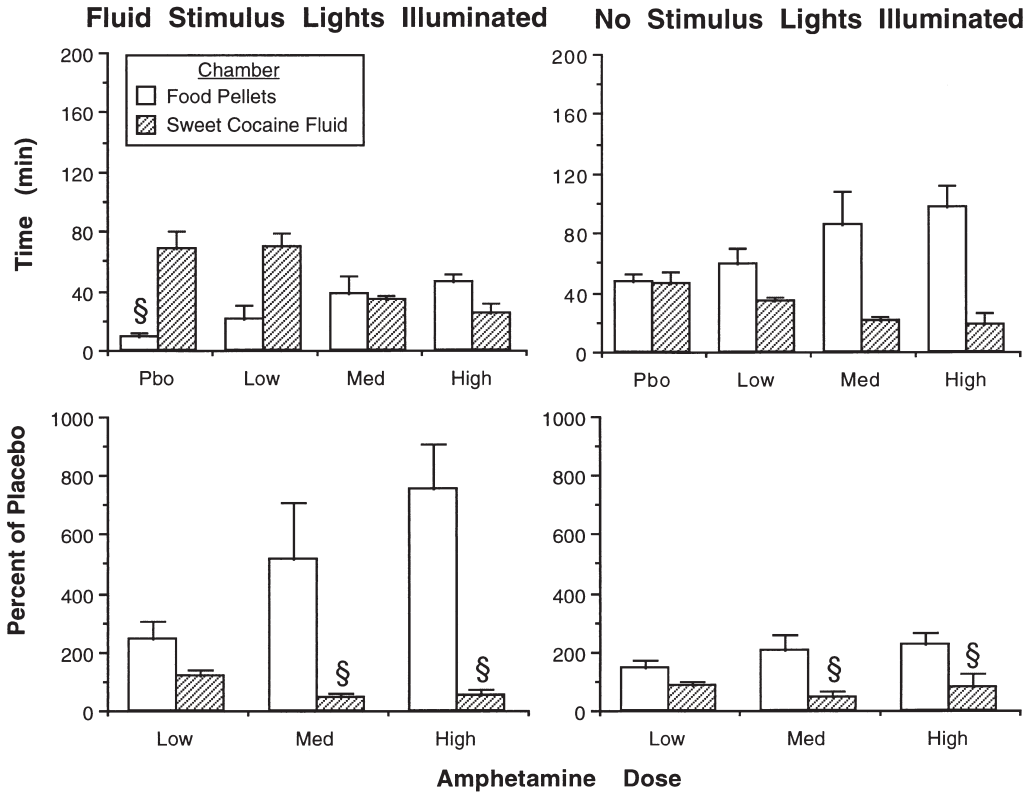

FIG. 4. Upper left panel: mean length of time monkeys spent in the food and sweet cocaine fluid chambers during sessions when fluid stimulus lights were illuminated as a function of AMPH dose condition. Upper right panel: mean length of time monkeys spent in the food and sweet cocaine fluid chambers during sessions when no stimulus lights were illuminated and no commodities were available as a function of AMPH dose condition. Lower panels: AMPH dose condition data from the above panels expressed as a percent of placebo baseline. See Fig. 1 for details.

for both food and cocaine (17). In the present study, responding maintained by a sweet cocaine fluid was decreased to a greater extent, even when corrected for differences in baseline intake, by AMPH than responding reinforced by food pellets. Because intake of a sweet fluid without cocaine was also decreased at a greater rate than food pellet intake (6), this greater decrease in sweet cocaine fluid intake may be related to the fluid as a reinforcer. Or, the greater rate of sweet cocaine fluid intake may represent a specific effect of AMPH on cocaine self-administration.

Unfortunately, relatively few studies have examined the effects of AMPH pretreatment on nondrug reinforcers using place-preference procedures. Although one report (1) found that AMPH did not alter novelty-induced CPP, in another study (2) apomorphine did alter novelty-induced CPP. Previous AMPH exposure has been shown to increase the rate of acquisition of cocaine self-administration (13) and to produce a CPP to low doses of cocaine that typically do not support a CPP (24), suggesting that AMPH may increase the ability of cocaine to condition a place preference. Clearly, that was not the case here. Thus, the increase in time spent in the food chamber following AMPH administration seems to have no precedent in the CPP literature.

Others (3,25) have noted that one difficulty in interpreting CPP is that preference for one side could also be avoidance of the other side. This appears to have been the case in our previous study (6). In that study, 1) monkeys spent more time in the food chamber than the fluid chamber under placebo conditions; 2) the increase in the length of time spent in the food chamber following AMPH was about twice as great as that observed here; and 3) the increase in time spent in the food chamber was significantly related to the decrease in the number of fluid deliveries. In fact, the decrease in fruit-drink deliveries accounted for 64% of the variance in time spent in the food chamber, when neither food nor fluid were available. In the present study, less than 10% of the variance in time spent in the food chamber was accounted for by the decrease in sweet cocaine fluid deliveries. Clearly the effects of AMPH on time spent in the food chamber were related to the alternative reinforcer (sweet cocaine fluid vs. fruit drink). This was not the case for the effects of AMPH on the number of second-order stimulus deliveries during the FI components and reinforcers delivered during the FR components, which were decreased similarly when either cocaine or a fruit drink were available.

The discrepancy between the self-administration and location-preference measures of reinforcement, i.e., less food self-administration and more food location preference, may not be related to the utility of these measures in assessing reinforcement. Rather, the discrepancy may be related to the differential sensitivity of these procedures to drug-induced disruptions in behavior. Furthermore, the choice to experience food sessions, rather than fluid sessions, was not affected by AMPH, further indicating that these multiple measures of reinforcement are differentially affected by drug administration. The present results were obtained with only one level of food reinforcement and one sweet cocaine fluid dose, so it is unclear what experimental variables may influence comparisons between self-administration and CPP measures of reinforcement.

It is also unclear if the present results may be due to an unspecified effect of AMPH, such as its ability to enhance responding reinforced by the presentation of stimuli previously paired with primary reinforcement [e.g., conditioned reinforcers, (21)]. If this were the case, then AMPH specifically enhanced the conditioned reinforcing effects of the location paired with food to a greater extent that the location paired with sweet cocaine fluid. Drugs that increase serotonin levels, such as dexfenfluramine, have been shown to decrease the conditioned reinforcing effects of stimuli paired with primary reinforcement (8). A study, using the current design, that tested the effects of a drug that increased serotonin levels on self-administration and location preference would provide valuable information about the potential mechanism of the dissociation between these measures of reinforcement.

Cocaine in a sweet-flavored solution was chosen as the alternative reinforcer to food because a previous study (9) indicated that it was an effective reinforcer. Compared with the results of our previous study on the effects of AMPH (6), the sweet cocaine fluid did engender different behavioral effects than a sweet fluid without cocaine: 1) the rate of responding during the FI components of sweet cocaine fluid sessions was nearly double that observed in our previous study for fruit-drink maintained responding; 2) monkeys spent more time in the sweet cocaine fluid chamber; 3) AMPH was less effective in decreasing sweet cocaine fluid intake than intake of fruit drink; and 4) the increase in time spent in the food chamber was not accounted for by the decrease in sweet cocaine fluid intake. Although not directly examined here, other studies have shown that oral cocaine can function as a reinforcer in self-administration studies in laboratory animals (7,16,18), and can condition a place preference in laboratory animals (20,24). In fact, one study showed that oral cocaine could produce a CPP in rats trained to self-administer oral cocaine using a schedule-induced technique (23).

In summary, pretreatment with AMPH decreased both food and sweet cocaine fluid self-administration, but increased location preference for the food chamber in the absence of stimuli associated with food availability. The increase in time spent in the food chamber was less than previously observed (6) when a sweet drink without cocaine was available during fluid sessions. These results indicate that 1) the relationship between self-administration and location preference measures of reinforcement is not completely concordant, 2) these two procedures may be differentially sensitive to pharmacological manipulations, and 3) the effects of pharmacological manipulations are dependent upon the two reinforcers being studied.

ACKNOWLEDGEMENTS

This research was supported by DA-08460 from The National Institute on Drug Abuse, and approved by the New York State Psychiatric Institute Animal Care and Use Committee. The assistance of Julian Perez, Rafael Salazar, Asiyah Rehman, and Drs. Mohamed Osman and Sandra Comer is gratefully acknowledged.

REFERENCES

1. Bardo, M. T.; Neisewander, J. L.; Pierce, R. C.: Novelty-induced place preference behavior in rats: Effects of opiate and dopaminergic drugs. Pharmacol. Biochem. Behav. 32:683–689; 1989.
2. Bardo, M. T.; Lacy, M.; Mattingly, B. A.: Effects of apomorphine on novelty-induced place preference behavior in rats. Pharmacol. Biochem. Behav. 37:89–93; 1990.

3. Bardo, M. T.; Rowlett, J. K.; Harris, M. J.: Conditioned place preference using opiate and stimulant drugs: A meta-analysis. Neurosci. Biobehav. Rev. 19:39–51; 1995.
4. Calcagnetti, D. J.; Keck, B. J.; Quatrella, L. A.; Schechter, M. D.: Minireview—Blockade of cocaine-induced conditioned place preference: Relevance to cocaine abuse therapeutics. Life Sci. 56:475–483; 1995.
5. Corwin, R. L.; Woolverton, W. L.; Schuster, C. R.; Johanson, C. E.: Anorectics: Effects on food intake and self-administration in rhesus monkeys. Alcohol Drug Res. 7:351–361; 1987.
6. Evans, S. M.; Foltin, R. W.: The effects of *d*-amphetamine on the reinforcing effects of food and fluid using a novel procedure combining self-administration and location preference. Behav. Pharmacol. 8:429–441; 1997.
7. Falk, J. L.; Lau, C. E.: Stimulus control of addictive behavior: Persistence in the presence and absence of a drug. Pharmacol. Biochem. Behav. 50:71–75; 1995.
8. Fletcher, P. J.: Effects of *d*-fenfluramine and metergoline on responding for conditioned reward and the response potentiating effect of nucleus accumbens *d*-amphetamine. Psychopharmacology (Berlin) 118:155–163; 1995.
9. Foltin, R. W.; Evans, S. M.: A novel protocol for studying food or drug seeking in rhesus monkeys. Psychopharmacology (Berlin) 132:209–216; 1997.
10. Foltin, R. W.; Fischman, M. W.: Food intake in baboons: Effects of *d*-amphetamine and fenfluramine. Pharmacol. Biochem. Behav. 31:585–592; 1988.
11. Foltin, R. W.; Schuster, C. R.: Interaction between the effects of intragastric meals and drugs on feeding in rhesus monkeys. J. Pharmacol. Exp. Ther. 226:405–410; 1983.
12. Hoffman, D. C.: The use of place conditioning in studying the neuropharmacology of drug reinforcement. Brain Res. Bull. 23:373–387; 1989.
13. Horger, B. A.; Shelton, K.; Schenk, S.: Pre-exposure sensitizes rats to the rewarding effects of cocaine. Pharmacol. Biochem. Behav. 37:707–711; 1990.
14. Hubner, C. B.; Koob, G. F.: Bromocriptine produces decreases in cocaine self-administration in the rat. Neuropsychopharmacology 3:101–108; 1990.
15. Kleven, M. S.; Woolverton, W. L.: Effects of bromocriptine and desipramine on behavior maintained by cocaine or food presentation in rhesus monkeys. Psychopharmacology (Berlin) 101:208–213; 1990.
16. Macenski, M. J.; Meisch, R. A.: Oral cocaine self-administration in rhesus monkeys: Strategies for engendering reinforcing effects. Exp. Clin. Psychopharmacol. 3:129–139; 1995.
17. Mansbach, R. S.; Balster, R. L.: Effects of mazindol on behavior maintained or occasioned by cocaine. Drug Alcohol Depend. 31:183–191; 1993.
18. Meisch, R. A.; Stewart, R. B.: Relative reinforcing effects of different doses of orally delivered cocaine. Drug Alcohol Depend. 37:141–147; 1995.
19. Mello, N. K.; Negus, S. S.; Lukas, S. E.; Mendelson, J. H.; Sholar, J. W.; Dreze, J.: A primate model of polydrug abuse: Cocaine and heroin combinations. J. Pharmacol. Exp. Ther. 274:1325–1337; 1995.
20. Nomikos, G. C.; Spyraki, C.: Cocaine-induced place conditioning: Importance of route of administration and other procedural variables. Psychopharmacology (Berlin) 94:119–125; 1988.
21. Robbins, T. W.; Watson, B. A. Gaskin, M.; Ennis, C.: Contrasting interactions of pipradrol, *d*-amphetamine, cocaine, cocaine analogues, apomorphine and other drugs with conditioned reinforcement. Psychopharmacology (Berlin) 80:113–119; 1983.
22. Schechter, M. D.; Calcagnetti, D. J.: Trends in place preference conditioning with a cross-indexed bibliography; 1957–1991. Neurosci. Biobehav. Rev. 17:21–41; 1993.
23. Seidman, M. H.; Lau, C. E.; Chen, R.; Falk, J. L.: Orally self-administered cocaine: Reinforcing efficacy by the place preference method. Pharmacol. Biochem. Behav. 43:235–241; 1992.
24. Shippenberg, T. S.; Heidbreder, C.: Sensitization to the conditioned rewarding effects of cocaine: Pharmacological and temporal characteristics. J. Pharmacol. Exp. Ther. 273:808–815; 1995.
25. Spyraki, C.; Nomikos, G. G.; Varonos, D. D.: Intravenous cocaine-induced place preference: Attenuation by haloperidol. Behav. Brain Res. 26:57–62; 1987.