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The effects of D-amphetamine on responding for candy and fruit drink using a fixed ratio and a progressive ratio schedule of reinforcer delivery

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Abstract

The first purpose of this study was to compare the effects of D-amphetamine (AMPH) on operant responding reinforced under fixed ratio (FR) or progressive ratio (PR) schedules of reinforcement, testing the hypothesis that responding reinforced under a PR operant schedule would be disrupted by lower doses of AMPH than responding reinforced under a FR operant schedule. The second purpose of this study was to test the generalizability of the first hypothesis by comparing the effects of AMPH on responding reinforced by two different reinforcers under both FR and PR operant schedules. Rhesus monkeys had five to six candy and five to six fruit-drink sessions per day, and could receive two reinforcers per session. Responding was initially reinforced under a PR procedure, such that the ratio size increased with each subsequent session. The parameters of the PR schedule were individually selected so that monkeys consumed a similar number of candy and fruit-drink reinforcers each day. The effects of oral AMPH (0.5, 0.75, 1.0 mg/kg) on responding were assessed. Responding was then stabilized using a FR schedule with parameters individually selected so that monkeys consumed a similar number of candy and fruit-drink reinforcers each day, and the effects of oral AMPH were again assessed. The PR breakpoint was significantly greater for candy than fruit-drink. AMPH produced dose-related decreases in both candy and fruit-drink intake, but each AMPH dose decreased the number of fruit-drink deliveries to a greater extent than the number of candy deliveries. The results failed to support the hypothesis that responding under PR schedules of reinforcement would be disrupted by lower doses of AMPH.

Keywords: Progressive ratio; Fixed ratio; D-Amphetamine; Reinforcement; Rhesus monkey

1. Introduction

Much information has been obtained about the neurochemical mechanisms underlying appetitive behavior by recording changes in appetitive behavior following the administration of pharmacological "challenges" (e.g., Terry et al., 1995; Witkin and Katz, 1990). Appetitive behavior of laboratory animals is commonly measured by recording responding on an operant manipulandum that is reinforced by the delivery of the commodity of interest, i.e., food in studies on feeding behavior (e.g., Ackroff and Sclafani, 1999; Reilly, 1999), water in studies of fluid intake (Mathis et al., 1996), and drug in studies on drug intake (LeSage et al., 1999).

The most common schedules of reinforcement used to maintain responding in operant studies of appetitive behavior are ratio schedules. Using ratio schedules, responding is maintained by the delivery of a reinforcer after completion of a predetermined number of responses (Ferster and Skinner, 1957). One variant of a ratio schedule requires the same number of responses for delivery of the reinforcer throughout the session, i.e., a fixed ratio (FR) schedule. Another common variant of a ratio procedure is a progressive ratio (PR) schedule of reinforcement. In a PR schedule, the number of responses required for delivery of the reinforcer systematically increases during the laboratory session (Hodos, 1961). Thus, the research organism makes a larger number of responses with each larger response requirement until the organism fails to complete a response requirement: The largest completed response requirement is known as the PR breakpoint. It is commonly assumed that a PR break-

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point provides a measure of the reinforcing efficacy of a reinforcer such that a larger PR breakpoint indicates a more efficacious reinforcer (e.g., Arnold and Roberts, 1997). For example, Roberts et al. (1989) concluded that the efficacy of intravenous (iv) cocaine as a reinforcer in female rats varied across the estrous cycle because PR breakpoints were greatest during estrus. By contrast, responding of male rats maintained by cocaine did not show a cyclical pattern in PR breakpoints.

In addition to basic research in appetitive behavior, these procedures are commonly used in laboratory animals to screen for potential therapeutic medications for excessive behavior such as overeating (obesity; Hagan et al., 1997; Roth and Rowland, 1998) and drug abuse (e.g., Williams and Woods, 1999). In the field of drug abuse, for example, (1) Mello and Negus (1998) and Negus et al. (1999) have reported many studies on the effects of drugs on responding reinforced by cocaine or food using FR schedules in rhesus monkeys and (2) we have reported on the effects of behavioral and pharmacological manipulations on responding reinforced by drugs of abuse using PR schedules in humans (Haney et al., 1997, 1998).

Previous studies from this laboratory have demonstrated that the effects of a range of anorectic drugs, including D-amphetamine (AMPH), on food intake of baboons were similar across a range of ratio requirements for pellet delivery (Foltin, 1993, 2000); increasing the response requirement or FR for food decreased food intake, but did not increase the sensitivity of responding to disruption by AMPH. In these studies, responding was stabilized for several days under each FR condition prior to testing AMPH, such that FR requirements changed across days. By contrast, the ratio requirement in PR schedules increases within days. The first purpose of the present study was to test the hypothesis that, because the ratio value changes within session under a PR schedule, responding reinforced under a PR operant schedule would be disrupted by lower doses of AMPH than responding reinforced under a FR operant schedule. Because the earlier data were collected in nonhuman primates, nonhuman primates were used in this study as well.

The second purpose of this study was to test the generalizability of the hypothesized relationship between changes in ratio requirements within days and disruption of responding by pharmacological manipulations. This was accomplished by examining responding reinforced by candy and responding reinforced by fruit drink in animals that were not food- or fluid-deprived. These two reinforcers were chosen because experience with these reinforcers using rhesus monkeys indicates that they have different reinforcing efficacy and thus, should engender responding with different PR breakpoints (Evans and Foltin, 1997; Foltin and Evans, 1997). In this way, it was possible to determine how reinforcer efficacy altered the effects of AMPH. Schedule parameters were adjusted between the PR and FR schedules of reinforcement in order to engender patterns of responding and reinforcer delivery that were similar between the two schedules. For example, the ratio values used in the FR and PR schedules were adjusted so that intakes of both commodities were similar, and the intertrial interval between trials under the FR schedule were increased during each day to mimic the increased intertrial intervals observed using PR schedules of reinforcement. In the present study, the effects of AMPH, an effective anorectic drug in humans and nonhuman primates (Blundell and Latham, 1980; Foltin, 1989; Foltin et al., 1995), which decreases food intake presumably by increasing release of catecholamines (Leibowitz, 1978), were determined because its anorectic effects are robust under a variety of experimental conditions.

2. Method

2.1. Animals and apparatus

Five adult male rhesus monkeys (*Macaca mulatta*), weighing between 7.9 and 9.5 kg at the start of the experiment, lived under the housing conditions described below. In addition to candy and fruit drink delivered under the operant schedule, each monkey received a daily chow ration designed to maintain a stable body weight (6–10 high-protein monkey diet no. 5047 chow, 3.37 kcal/g; LabDiets, PMI Feeds, St. Louis, MO), chewable vitamins, and a piece of fruit daily. Body weights, determined weekly, remained stable throughout the study. Monkeys were housed in customized, squeeze-capable, rack-mounted, nonhuman primate cages (Hazleton Systems, 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 $\times$ 40 cm openings. For three of the monkeys, sweet fruit-drink self-administration occurred in the left-end chamber and candy 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. 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 0700 to 1900 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 candy response panel also had a food hopper, a pair of green lights over the hopper, and a pellet dispenser (model PDC-005, BRS-LVE) mounted on the outside. The fruit-drink 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, Chicago, IL) and a fluid source mounted on the outside.

2.2. Operant schedule

Responding maintained by candy or fruit drink was reinforced according to a two-component chained schedule of reinforcement with responding during each component on a separate lever (Evans and Foltin, 1997; Foltin and Evans, 1997). The first component, signalled by a yellow light over the left lever, was a fixed-ratio (FR) 1. The first response 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 schedule with a 30-s time out (TO) after reinforcer delivery, when responding had no programmed consequences [FR (TO 30 s)]. Responding in the candy chamber was reinforced by the delivery of five plain chocolate M&Ms (Mars, Hackettstown, NJ; 4.5 g, 22 kcal: 3 g carbohydrate, 1 g fat, 0.2 g protein). Responding in the fruit-drink chamber was reinforced by 5 ml of a 0.25-kcal/ml dilute strawberry–raspberry-flavored solution [260 g glucose (3.85 kcal/g, Sigma, St. Louis, MO) dissolved in 4000 ml tap water with one packet of Incrediberry Kool-Aid (Kraft General Foods, White Plains, NY)]. Two reinforcer deliveries could be earned during each session.

During training, monkeys had five to six candy and five to six fruit-drink sessions per day with a 3-h interval between candy and fruit drink sessions; order of candy or fruit-drink sessions was varied among monkeys. Data were collected 7 days a week. The FR requirement during the first candy and fruit-drink session was initially 30. The FR size increased with each subsequent session, with the size of the increase varying for each commodity as training progressed. Thus, responding for both commodities was shaped under a PR procedure modeled after that reported by Rowlett and Woolverton (1997), except that in the current study, two reinforcer deliveries could be earned at each cost compared to four deliveries in the studies by Rowlett and Woolverton. The size of the initial ratio and the increment in subsequent ratios was increased until stable responding was observed and all monkeys failed to complete the ratio requirement of one of the sessions. Based on individual differences in breakpoint (value of last completed ratio), the final schedule parameters varied across monkeys and reinforcers. The ratio requirements for candy delivery tested with (1) Monkeys M and Z were 60, 120, 240, 480, and 960, (2) Monkeys A and W were 60, 120, 240, 480, 960, and 1440, and (3) Monkey S were 30, 60, 120, 240, 480, and 960. The ratio requirements for fruit-drink delivery tested with (1) Monkeys S, M, and Z were 30, 60, 120, 240, and 480 and (2) Monkeys A and W were 30, 60, 120, 240, 480, and 960. Lower initial ratio values were used when fruit drink was the reinforcer (and when candy was the reinforcer in Monkey S) in order to provide similar numbers of sessions and total daily number of reinforcers for candy and fruit drink. There was a limited hold in effect during each session, such that monkeys had to complete the ratio requirement (once or twice) within a set period. The limited hold duration increased with increasing ratio requirement (FR30, FR60, FR120, FR240, FR480: 15 min; FR960: 20 min; FR1440: 30 min). Because of existing equipment and programming limitations, the PR sessions advanced even after a monkey stopped responding. Thus, under test conditions, it was possible that several sessions occurred after a monkey stopped responding. By using the chained schedule, requiring a monkey to respond to activate the lever and stimulus lights associated with reinforcement, during the sessions that a monkey did not respond the stimulus lights associated with the PR schedule were not presented.

The effects of oral AMPH sulfate (0.5, 0.75, 1.0 mg/kg; Sigma) on responding reinforced by candy and fruit drink were assessed in all five monkeys. Approximately twice a week, animals had test days, usually Mondays and Thursdays, assuming candy and fruit-drink intake were stable on the previous days (no upward or downward trend in the data compared to previous nondrug days). On these test days, monkeys were given an oral pretreatment of AMPH 30 min before the start of the daily session in the middle chamber. The appropriate amount of AMPH stock solution (10 mg/ml concentration) was added to 40–60 ml of concentrated Kool-Aid (Tropical Punch flavor made with 20% of the water recommended) and administered orally via vinyl tubing, which functioned like a straw. On nontest days, except Sunday, monkeys were given the concentrated Kool-Aid solution without AMPH (i.e., placebo) before the daily session. Monkeys consumed the entire amount of fluid using this procedure. Responding for candy and fruit drink was stable (no increasing or decreasing trends based on mean total daily responding and mean number of candy and fruit-drink deliveries for each monkey) for at least 2 weeks before the dose–response functions for AMPH were conducted. After completion of the first dose–response function, the order of daily candy and fruit-drink sessions was switched, so that the monkeys who initially experienced candy sessions first, had the fruit-drink sessions first and vice versa for the monkeys who initially experienced fruit-drink sessions first. The dose–response function for AMPH was then again determined after responding had stabilized for all monkeys.

Responding was then stabilized using the same FR schedule of reinforcer delivery during each session: The ratio for each reinforcer was the initial ratio used for each monkey when responding was reinforced using the

PR schedules. Under the PR schedule, more time was required to fulfill each successive ratio requirement such that the interval between sessions of reinforcer deliveries increased with increasing ratio requirement. In order to approximate the increasing intervals experienced under the PR condition, a TO was programmed between each successive candy or fruit-drink FR session. During the TO, responding was recorded but had no programmed consequences. The TO after the first session for each commodity was 150 s, and the length doubled after each subsequent session. Responding for candy and fruit drink was stable for at least 2 weeks before the dose–response functions for AMPH were conducted. As described above, when responding was reinforced using the PR schedules, each dose of AMPH was tested twice: once when the day began with the five to six candy sessions and once when the day began with the five to six fruit-drink sessions.

2.3. Data analysis

The total number of reinforcers earned each day, i.e., up to two during each session for a maximum of 12, was analyzed using a four-factor repeated-measures ANOVA with schedule as the first factor (FR vs. PR), test type as the second factor (candy first vs. fruit drink first), AMPH dose as the third factor, and reinforcer as the fourth factor (candy vs. fruit drink). The placebo values for each schedule were obtained by averaging the data obtained on the placebo day that preceded each of the six active AMPH doses to yield a single placebo value. To control for possible differences in absolute number of reinforcers earned under each schedule for candy and fruit drink, these data were also analyzed as a proportion of baseline. Breakpoint obtained during the PR portion of the study was analyzed using a three-factor repeated-measures ANOVA with test type as the first factor, AMPH dose as the second factor and reinforcer as the third factor. Results for all analyses were considered significant at $P<.05$, using Hunyh–Feldt corrections where appropriate. Post hoc comparisons were accomplished using single degree of freedom contrasts.

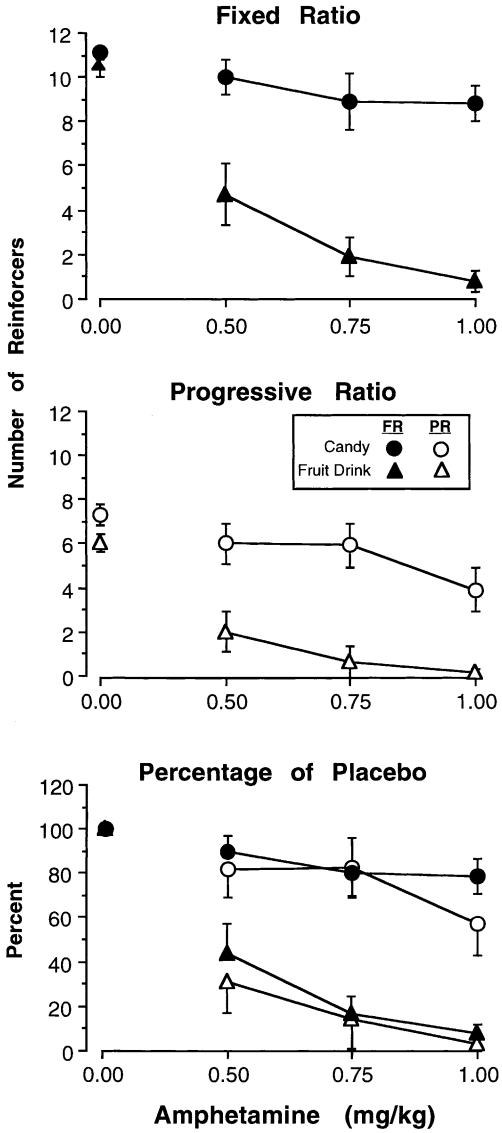

Fig. 1. Upper panel: Total mean number of reinforcer deliveries each experimental day when responding was maintained using FR schedules of candy and fruit drink delivery as a function of AMPH dose. Middle panel: Total mean number of reinforcer deliveries each experimental day when responding was maintained using PR schedules of candy and fruit drink delivery as a function of AMPH dose. Bottom panel: AMPH dose data from the above panels expressed as a percent of placebo baseline. Error bars represent 1 S.E.M.

3. Results

Fig. 1 shows the total number of reinforcers delivered during candy and fruit drink sessions when responding was maintained using FR (top panel) or PR (middle panel) schedules as a function of AMPH dose. Under placebo conditions, monkeys earned a similar number of candy and fruit-drink deliveries each day under both FR ($P>.39$) and PR ($P>.14$) conditions. AMPH produced a dose-related decrease in the number of reinforcer deliveries [$F(3,12)=42.6$, $P<.0001$]. Although it was possible for a monkey to skip a session and move on to the next session, i.e., under the PR schedule a monkey could not respond at a smaller ratio value, but could respond at a larger ratio value, although this never happened. Monkeys completed the sessions sequentially, and once responding under either schedule had stopped, no monkey responded again during the experimental day. There were no significant effects of session order (candy vs. fruit drink first). There was a significant dose by reinforcer interaction [$F(3,12)=12.1$, $P<.0006$], indicating that the slope of the AMPH dose–response function varied between the two reinforcers. Post hoc comparisons

indicated that when responding was reinforced with candy under the FR schedule (1) 0.50 mg/kg AMPH decreased fluid [$F(1,12)=48.8$, $P<.0001$], but not candy intake, (2) 0.75 mg/kg AMPH decreased both fluid [$F(1,12)=108.5$, $P<.0001$] and candy intake [$F(1,12)=7.7$, $P<.022$], and (3)1.00 mg/kg AMPH decreased both fluid [$F(1,12)=138.4$, $P<.0001$] and candy intake [$F(1,12)=7.9$, $P<.018$]. Post hoc comparisons indicated that when responding was reinforced with candy under the PR schedule (1) 0.50 mg/kg AMPH decreased fluid [$F(1,12)=24.1$, $P<.0005$], but not candy intake, (2) 0.75 mg/kg AMPH decreased fluid [$F(1,12)=43.78$, $P<.0001$], but not candy intake, and (3)1.00 mg/kg AMPH decreased both fluid [$F(1,12)=52.3$, $P<.0001$] and candy intake [$F(1,12)=17.4$, $P<.018$]. Thus, the dose–response functions for the effects of AMPH on fruit-drink intake were shifted to the left of the dose–response functions for the effects of AMPH on candy intake under both schedules of reinforcement.

The AMPH data shown in the top two panels of Fig. 1 are regraphed as percent change from placebo-dose baseline in the bottom panel of Fig. 1. When analyzed as percentage of placebo, AMPH produced a dose-related decrease in the percentage of reinforcer deliveries [$F(2,8)=8.64$, $P<.01$], with a significantly greater decrease in percentage of deliveries occurring during fruit drink compared to candy deliveries [$F(1,4)=71.1$, $P<.001$]. Post hoc comparisons failed to reveal any significant differences in the effects of AMPH between the FR and PR conditions.

Fig. 2 shows the PR breakpoint for responding reinforced with candy and fruit drink as a function of AMPH dose. Under placebo conditions, the PR breakpoint for candy (672) was about three times the breakpoint for fruit drink [216, $F(1,12)=19.1$, $P<.01$]. AMPH produced a dose-related decrease in PR breakpoint [$F(3,12)=7.5$, $P<.004$], with the breakpoint for fruit drink being significantly less than the breakpoint for candy at all AMPH doses [$F(1,4)=11.6$, $P<.027$]. When the effects of AMPH were converted to change from baseline, the three AMPH doses decreased the PR breakpoint for candy to 60%, 54%, and 37% of baseline. By contrast, when the effects of AMPH were converted to change from baseline, the three AMPH doses decreased the PR breakpoint for fruit drink to 37%, 11%, and 2% of baseline.

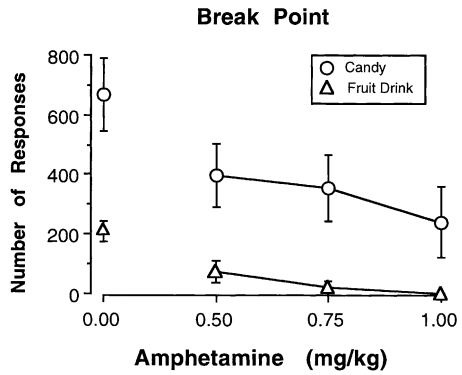

Fig. 2. Mean PR breakpoint when responding was maintained using PR schedules of candy and fruit drink delivery as a function of AMPH dose.

4. Discussion

The results of the present study clearly show that (1) the PR breakpoint was significantly greater for candy than fruit drink, (2) AMPH produced dose-related decreases in both candy and fruit-drink intake, (3) there was a significant interaction between AMPH dose and reinforcer, such that at each dose, AMPH produced a greater decrease in fruit-drink intake than candy intake, and (4) the effects of AMPH on candy and fruit-drink intake did not vary between the FR and PR operant schedule conditions.

The finding that AMPH had similar effects on responding under both FR and PR schedules of reinforcement failed to confirm the hypothesis that responding under the PR schedule would be disrupted by lower doses of AMPH. These results extend previous findings from this laboratory using FR schedules, which demonstrated that the effects of anorectic drugs on food intake of baboons were similar across FR requirements (Foltin, 1993, 2000) to responding under PR schedules of reinforcement. Furthermore, because the effects of AMPH on responding reinforced by candy and fruit drink were similar across the PR and FR schedules of reinforcement, these effects cannot be accounted for by a unique interaction between one reinforcer and the two ratio schedules. Thus, regardless of the reinforcer, both FR and PR schedules of reinforcement provided a behavioral baseline that was similarly disrupted by a range of AMPH doses.

The PR breakpoint was significantly greater for candy than fruit drink, suggesting that candy had greater reinforcing efficacy than fruit drink. In addition, smaller ratio values were used with fruit drink than candy under the FR schedule further indicating that fruit drink is a less efficacious reinforcer than candy (Bickel et al., 1993; Hursh, 1984). This difference in PR breakpoint and FR value may account for the finding that the AMPH dose–response function when fruit drink was available was shifted to the left of the AMPH dose–response function when candy was available. Responding that is maintained with reinforcers that engender lower PR breakpoints is more easily disrupted by pharmacological manipulations. Although, because some monkeys did not work at all for fruit drink after receiving the largest AMPH dose, there may have been a floor effect. This could be addressed by using a PR schedule that started with a smaller initial value than used here.

Caine and Koob (1995) also conducted a study that compared the effects of a pharmacological manipulation on responding reinforced under FR and PR schedules of reinforcement. Although this study used a different reinforcer than that used here, it provides information directly comparing the effects of a pharmacological manipulation on

responding reinforced using FR and PR schedules of reinforcement. 7-OH-DPAT produced dose-dependent decreases in intravenous cocaine intake (0.25 mg/kg/infusion) by increasing the interval between reinforcer deliveries when responding was maintained using an FR5 schedule of reinforcement. The largest dose of 7-OH-DPAT, which produced an approximately 50% decrease in cocaine intake (0.25 mg/kg/infusion) using the FR schedule of reinforcement, did not alter the PR breakpoint for 0.25 mg/kg cocaine. There was, however, a nonsignificant trend for 7-OH-DPAT to increase the PR breakpoint for all the cocaine doses. The differential sensitivity of the FR and PR schedules of reinforcement in the Caine and Koob (1995) study may have been caused by the procedural differences between the two schedules (e.g., PR session lasted 12 h, while the FR session lasted 3 h), or the use of self-administered drug as the reinforcers. It is also possible that the PR schedule was less affected by the increase in the interinfusion interval following 7-OH-DPAT administration. In the present study, an increasing interval was programmed between successive FR sessions in order to control for the extra time required to complete the ratio requirement with each increase in PR requirement.

In contrast to the Caine and Koob (1995) study, but similar to the present study, Kushner et al. (1999) reported that an irreversible inhibitor of GABA transmission produced similar decreases in the number of cocaine infusions self-administered by rats using either FR or PR schedules. Similar decreases were also seen in the number of food deliveries received by rats using either FR or PR schedules. In both the Kushner et al. (1999) study and the present study, similar session lengths were used regardless of the reinforcement schedule used to maintain responding.

As mentioned in Section 1, changes in the PR breakpoint are commonly interpreted as changes in the reinforcing efficacy of the maintaining event, e.g., a decrease in breakpoint following a pharmacological manipulation is interpreted as a decrease in the reinforcing efficacy of the reinforcer (e.g., Rowlett and Woolverton, 1997; Stafford et al., 1998). The results of the present study indicate that, under certain conditions, responding using FR and PR schedules provides similar information. This should not be surprising since both FR and PR schedules are based on the number of responses. Thus, the effects of pharmacological and behavioral manipulations on responding maintained using either FR or PR schedules of reinforcement provide information about the reinforcing efficacy of the appetitive reinforcer.

The FR schedule and the initial ratio value of the PR schedule used in the present study were chosen to provide similar levels of reinforcer delivery for the two commodities under baseline conditions. In this way, any observed differential effects of AMPH on fruit drink and candy intake would not be brought about by baseline differences in number of reinforcers delivered each day (e.g., rate effects; Kelleher and Morse, 1968). Incrementing TOs between reinforcer availability in the FR schedule were also implemented in an attempt to provide similar baseline temporal patterns of reinforcer delivery under both FR and PR schedules. Unfortunately, it was not possible to equate the total number of reinforcers delivered per day under the PR (about 11) and FR (about 7) schedules of reinforcement. These schedule parameters, unique to this study, the use of a chained schedule, and the use of nonhuman primates, were most likely important in generating behavior that was similarly disrupted by AMPH under the FR and PR schedules. Furthermore, these unique study and schedule parameters may limit the generalizability of the results.

In conclusion, AMPH produced dose-dependent decreases in candy and fruit-drink consumption, and, although the dose–response functions for the effects of AMPH on fruit drink intake were shifted to the left of the dose–response functions for candy intake, the effects of each AMPH dose on fruit-drink and candy intake did not differ between FR and PR schedules.

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