Effects of Phentermine on Responding Maintained under Multiple Fixed-Ratio Schedules of Food and Cocaine Presentation in the Rhesus Monkey

FRANCIS H. E. WOJNICKI, RICHARD B. ROTHMAN, KENNER C. RICE and JOHN R. GLOWA

ABSTRACT

Drugs that decrease drug-maintained responding at doses that do not decrease other behaviors in animals may be suitable candidates for development as medications to treat drug abuse in humans. The present study examined whether this effect could be obtained with phentermine, a drug that has been reported to decrease cocaine intake in humans. Rhesus monkeys were trained under multiple fixed-ratio 30-response schedules of food and i.v. cocaine delivery. Phentermine was always given as a slow, i.v. infusion. Acute treatment with phentermine (0.3–10 mg/kg) decreased cocaine-maintained responding at doses that did not decrease, or decreased less, food-maintained responding for each of three unit doses of cocaine (10–100 µg/kg/injection). Subacute treatment with phentermine (3 or 5.6 mg/kg, daily) also decreased cocaine-maintained responding more than food-maintained responding.

There is current interest in whether pharmacological treatments can be developed that will decrease cocaine abuse in humans. One approach to assessing this possibility is to test potential treatments on behaviors associated with the abuse potential of cocaine (Woolverton and Kleven, 1991). A number of reports have shown that cocaine self-administration can be decreased by drug treatment. However, high doses of any drug can decrease any behavior, questioning whether these drug-induced decreases in cocaine self-administration are behaviorally specific. Some drugs decrease cocaine self-administration at doses that have less of an effect on comparable rates of food-maintained responding. For example, buprenorphine (Mello et al., 1989), SKF 38393 (Katz and Witkin, 1992), GBR 12909 (Glowa et al., 1995a), and CFT (Glowa and Wojnicki, 1996) decrease responding maintained by cocaine at doses that have little or no effect on food-maintained responding. The difference in effect of these drugs on food- and cocaine-maintained responding suggests that self-administration was not decreased due to a nonspecific effect of drug treatment, as a nonspecific effect would be expected to decrease both behaviors. However, several additional interpretations of these decreases in cocaine self-administration remain.

If drug treatments selectively affect the potency of cocaine, they could decrease responding maintained by peak unit doses of cocaine without affecting food-maintained performances. Dopamine (DA) antagonists clearly shift the unit dose-effect function for cocaine to the right (Bergman et al., 1990; Glowa and Wojnicki, 1996), suggesting that they decrease the potency of cocaine. Some (Caine and Koob, 1995), on comparable rates of food-maintained responding. For example, buprenorphine (Mello et al., 1989), SKF 38393 (Katz and Witkin, 1992), GBR 12909 (Glowa et al., 1995a), and CFT (Glowa and Wojnicki, 1996) decrease responding maintained by cocaine at doses that have little or no effect on food-maintained responding. The difference in effect of these drugs on food- and cocaine-maintained responding suggests that self-administration was not decreased due to a nonspecific effect of drug treatment, as a nonspecific effect would be expected to decrease both behaviors. However, several additional interpretations of these decreases in cocaine self-administration remain.

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but not all (Glowa et al., 1995a; Glowa and Wojnicki, 1996) functional DA agonists can shift the unit dose-effect function for cocaine to the left. Further studies will be necessary to determine whether DA agonists decrease self-administration by affecting the potency of cocaine.

Drug treatment may decrease the reinforcing effects of cocaine. A number of procedures have been used to provide a metric of the reinforcing effects of drugs including progressive-ratio performances, choice situations, and the acquisition or extinction of responding (Katz, 1990). Lesions of specific brain structures (e.g., Caine and Koob, 1994), certain drugs (e.g., Roberts and Richardson, 1982), or access to alternative reinforcers (e.g., Nader and Woolverton, 1991) can decrease these measures of the reinforcing effects of cocaine. However, few studies have determined whether drugs decrease these measures for other events to an extent comparable to that seen for cocaine.

Drug treatment may also decrease responding that is less resistant to change (Nevin, 1974) more than responding maintained under other conditions. For example, Egli et al. (1992) showed that the same dose of a drug decreases responding maintained by relatively low densities of food presentation more than responding maintained by higher densities of food presentation. Other studies have reported that doses of several drugs decrease responding maintained by low unit doses of cocaine more than responding maintained by high unit doses (Caine and Koob, 1995; Glowa et al., 1995a; Mello and Negus, 1996). These results suggest that responding maintained by events with greater reinforcing efficacies are more resistant to change. If food is a more effective reinforcer, drug treatment could decrease cocaine self-administration without affecting food-maintained responding.

Because few studies have studied a sufficient range of conditions to address these interpretations, the current experiments were designed to assess the effects of drug treatment on responding maintained by food and several different unit doses of cocaine. Phentermine was chosen because preliminary data suggested it could decrease cocaine-maintained responding at doses that had less of an effect on food-maintained responding (Glowa et al., 1997). Phentermine is an indirect DA agonist thought to exert its effects primarily by increasing the release of DA (Rothman et al., 1996). It has been given in combination with fenfluramine (fen-phen) to decrease food intake in obese humans (Weintraub et al., 1984). Similarities between excessive food and drug intake led Hitzig (1993) to propose the use of this drug combination as a medication for drug abuse, although there have been recent concerns regarding its safety (Mark et al., 1997). A case study suggested phentermine was effective in decreasing cocaine intake in humans (Rothman et al., 1994). Thus, an additional purpose of the present studies was to determine if a drug that was effective in decreasing cocaine intake in humans could decrease cocaine-maintained responding in laboratory animals at doses that did not affect food-maintained responding.

Materials and Methods

Subjects. Eleven adult male rhesus monkeys (Macaca mulatta; nos. 31, 44, 72, 675, 872, 522, 573, 561, 941, 769, and 450), weighing 6.8 to 9.0 kg were studied. Each monkey was maintained at approximately 90% of its free-feeding weight. All monkeys had been previously trained to sit in a restraint chair (Primate Products, Redwood City, CA) during experimental sessions and had previous experience with FR schedules of food, cocaine (1–100 μg/kg/injection), and in some cases (monkey nos. 675, 872, 573, 561, 941, and 769), GBR 12909 delivery. All animals had previous experience with GBR 12909 pretreatment, and some animals had previous experience with GBR 12935 (no. 561), d-amphetamine and CPT (nos. 72, 31, and 44), or single/combined doses of phentermine and fenfluramine (nos. 675, 872, 522, and 573) pretreatment.

Apparatus. Monkeys responded in one of four enclosed operant chambers that were approximately 60 cm wide × 100 cm high × 90 cm deep. Each chamber was equipped with a ventilating fan, house light, and an aluminum panel facing the monkey. The panel was equipped with two response levers (BRS/LVE, Beltsville, MD), four pairs of lights, and a water spout. Response levers were modified by removing the standard “paddle” and replacing it with a solid aluminum (1 × 3 × ½ inches) paddle, which pivoted on a pair of pins. A downward force of about 20g (0.196 N) on either lever produced an audible click of a feedback relay and a response. Food (1-g banana pellets; P.J. Noyes Co., Lancaster, NH) was delivered by a solenoid-activated food pellet dispenser (BRS/LVE) to the receptacle immediately in front of the monkey 10 cm above the waist plate. An indwelling i.v. jugular catheter and vascular-access port (Access Technologies, Skokie, IL) was implanted in each monkey (Glowa et al., 1995a,b). A sterile infusion line connected the vascular-access port to a syringe driver. Events were programmed by a computer system (MED-PC) and monitored on cumulative recorders.

Procedure. Animals were trained to exit the cage and to sit in a restraint chair using a pole and collar technique. They were then weighed, placed in the chamber, and the area over the port was scrubbed with betadine and alcohol. The port was accessed with a syringe fitted with a huber-point needle. Before the start of each session (after presession drug administration), the port and catheter were first flushed with saline and then filled with the drug reinforcer (cocaine or GBR 12909).

Animals were previously trained under two variants of a mult FR 30-response (FR30) food, FR30 cocaine schedule of reinforcement (Glowa et al., 1995a; 1997). Under each variant, 30 responses in the presence of red stimulus lights produced a food delivery; 30 responses in the presence of blue stimulus lights produced a drug (cocaine or GBR 12909) delivery. Each reinforcer delivery was followed by a 3-sec time-out (TO), during which all stimuli were turned off and responding had no programmed consequences. Each FR30 was constrained by a 60-sec LH, such that if 30 responses were not emitted within 60 sec, the availability of a reinforcer was terminated, a 3-sec TO was produced, and both the FR requirement and the LH time were reset. Food or drug availability was limited to discrete components within a session. Each component limited the availability of reinforcers to a maximum of 10. Components terminated when 10 reinforcers, 10 LHs, or any combination of the two to total 10 occurred. Food and drug components strictly alternated and were separated by a TO. In the variant used to assess the acute and subacute effects of phentermine, the session began with a 15-min TO, followed by a food component, a 5-min TO, and then a cocaine component; two food pellets were delivered as each reinforcer in the food component. In the variant used to assess the effects of phentermine on responding that produced a low unit dose of cocaine or GBR 12909, the session began with a food component, followed by a 10-min TO, a drug component, and then a 10-min TO; one food pellet was delivered as each reinforcer in the food component. One session, consisting of four cycles of either sequence, was conducted daily. Total session times depended upon rates of responding, but control sessions typically required a minimum of 90 min. Sessions were conducted daily, 5 to 7 days a week. Phentermine was always given before the session, by slow infusion (see drugs).

Acute Assessment. This experiment assessed the effects of a range of acute doses (0.3–10 mg/kg) of phentermine on responding
maintained by food and different unit doses of cocaine. Acute assessments typically occurred on Tuesdays or Fridays, and control data were obtained from the four to nine intervening sessions on Thursdays. Doses of phentermine were usually tested at least twice. Responding of monkey nos. 872, 522, 675, and 573 was maintained at 10 μg/kg/injection cocaine until stable, and then the effects of phentermine were assessed. The unit dose was then increased to 30 μg/kg/injection cocaine, responding was allowed to stabilize, and the effects of phentermine were determined again. Doses higher than those necessary to almost completely decrease cocaine-maintained responding were not given to individual animals. The unit dose was then decreased to 10 μg/kg/injection cocaine, and the effects of subacute phentermine were determined (see below). After the subacute assessment, the unit dose was increased to 100 μg/kg/injection cocaine, responding was allowed to stabilize, and the effects of phentermine were determined. Monkey no.675 was not studied at 100 μg/kg/injection cocaine.

**Subacute Assessment.** This experiment assessed the effects of repeated daily doses of phentermine on food- and cocaine-maintained responding. Responding of monkey nos. 872, 522, 675, and 573 was maintained at 10 μg/kg/injection cocaine until stable. Control rates of responding were taken from three sessions immediately preceding the assessment of the effects of an acute dose of 5.6 mg/kg phentermine. The subacute effects of 5.6 mg/kg phentermine were then assessed for the following six to eight consecutive sessions in a manner identical to that described for acute dosing. The subacute effects of 3 mg/kg phentermine were then assessed during the following four to eight sessions. The subacute effects of saline were then assessed during the next four sessions. Finally, the acute effects of 5.6 mg/kg phentermine were re-determined in the next session.

**Low Unit-Dose Assessment.** Two experiments assessed the effects of phentermine when responding produced a low unit dose of cocaine. In the first experiment, responding of monkey nos. 31, 44, and 72 was maintained under a mult schedule with a unit dose of 10 μg/kg/injection cocaine until stable, then the unit dose was decreased to 1 μg/kg/injection. When rates of responding in the cocaine component had decreased compared with those during the 10 μg/kg/injection unit dose of cocaine, 3 mg/kg phentermine was given before the next session. On subsequent Tuesdays and Fridays (except for the last dose of 1 mg/kg), the effects of 1.7 mg/kg, 1 mg/kg, 0.3 mg/kg, and then 1 mg/kg phentermine were assessed. For the second experiment, responding of monkey nos. 31, 44, 522, and 72 was maintained under a mult schedule with a unit dose of 10 μg/kg/injection cocaine until stable. Then the unit dose was decreased to 1 μg/kg/injection, and an FR30 cocaine (1 μg/kg/injection), TO-20 min schedule was placed into effect (i.e., food-maintained responding was not studied, and a 20-min TO was used to keep session lengths comparable to those of the first experiment). When rates of responding had decreased compared with those in the cocaine component during the preceding baseline (10 μg/kg/injection unit dose of cocaine) conditions, 1 mg/kg phentermine was given before the next session. After two intervening sessions without infusions, the effects of 1 mg/kg were reassessed.

**Assessment on GBR 12909-Maintained Responding.** This experiment assessed the effects of phentermine on responding maintained by food and GBR 12909. Responding of four monkeys (nos. 561, 941, 769, and 450) was maintained under a mult FR30 food, FR30 GBR 12909 (30 μg/kg/injection) schedule until stable. The effects of a range of acute doses of phentermine were then studied. Acute assessments typically occurred on Tuesdays or Fridays, and control data were obtained from sessions on five intervening Thursdays. Doses of phentermine were tested at least twice.

**Data Analysis.** For each experiment, session rates of responding were calculated for each type of component (food or drug) and averaged over consecutive control sessions to provide an average rate of responding per component type, per monkey. Stability during baseline conditions was defined as no trend in rate of responding and at least three consecutive sessions when mean rates in the cocaine component varied less than 20%. Control data were typically taken from all sessions on Thursdays over the period when animals were dosed on Tuesdays and Fridays. Control data were expressed either as the mean (± S.D.) absolute response rate (resp/sec) or reinforcer deliveries, or as a mean ± coefficient of variation [(SD/mean) × 100] for percent of control data. Changes in within-session performance were characterized by the number of reinforcer deliveries to occur in each component.

**Drugs.** GBR12909-2HCl (1-[2-bis(4-fluorophenyl)methoxy-ethyl]-4-[3-phenylpropyl] piperazine) was synthesized by the Laboratory of Medicinal Chemistry/National Institute of Diabetes and Digestive and Kidney Diseases/National Institutes of Health. Cocaine was provided by the National Institute on Drug Abuse (Rockville, MD). Both drugs were dissolved in sterile water, diluted with saline, and delivered (0.75 ml/10 kg, i.v.) at a rate of 0.27 ml/sec. Unit doses were manipulated by changing the concentration (10 μg/kg/injection = 133 mg/liter). Phentermine (Sigma, St. Louis, MO) was dissolved in saline and delivered as a slow (~2 ml/min) i.v. infusion beginning 30 min before a session, for approximately 15 min (i.e., the infusion terminated about 15 min before the session began). All dose calculations were based on the salt.

### Results

**Acute Assessment.** Control rates of responding and numbers of reinforcer deliveries for both food and cocaine when different unit doses (10, 30, and 100 μg/kg/injection) of cocaine-maintained responding are shown in Table 1. When the unit dose was 10 μg/kg/injection, rates of responding in both the food component and the cocaine component were relatively high and similar to each other. At 10 μg/kg/injection, all 40 food deliveries and almost all the cocaine deliveries were obtained. When the unit dose was 30 μg/kg/injection, the average rate of responding in the food component was similar to food-maintained rates when the unit dose was 10 μg/kg/injection, but rates of responding in the cocaine component were decreased. At 30 μg/kg/injection, almost all food deliveries were obtained, but the number of cocaine deliveries was decreased about 25%. When the unit dose was 100 μg/kg/injection, the average rate of responding in the food

<table>
<thead>
<tr>
<th>Monkey no.</th>
<th>Fd RR</th>
<th>Coc RR</th>
<th>Fd Del</th>
<th>Coc Del</th>
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<tr>
<td>675</td>
<td>7.56 ± 0.37</td>
<td>7.28 ± 0.74</td>
<td>40.0 ± 0</td>
<td>40.0 ± 0</td>
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<td>872</td>
<td>5.74 ± 0.57</td>
<td>2.46 ± 0.55</td>
<td>40.0 ± 0</td>
<td>38.6 ± 0.7</td>
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<td>522</td>
<td>2.46 ± 0.23</td>
<td>2.66 ± 1.05</td>
<td>40.0 ± 0</td>
<td>37.4 ± 3.0</td>
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<tr>
<td>573</td>
<td>4.08 ± 0.33</td>
<td>3.03 ± 0.62</td>
<td>40.0 ± 0</td>
<td>37.2 ± 4.7</td>
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<tr>
<td>Group</td>
<td>4.95 ± 0.38</td>
<td>3.86 ± 0.74</td>
<td>40.0 ± 0</td>
<td>38.3 ± 2.3</td>
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<th>Coc Del</th>
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<td>675</td>
<td>9.05 ± 0.52</td>
<td>2.95 ± 1.74</td>
<td>40.0 ± 0</td>
<td>27.2 ± 3.8</td>
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<td>872</td>
<td>5.26 ± 0.92</td>
<td>3.33 ± 1.12</td>
<td>40.0 ± 0</td>
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<td>522</td>
<td>2.86 ± 0.53</td>
<td>1.83 ± 0.45</td>
<td>40.0 ± 0</td>
<td>27.7 ± 4.1</td>
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<td>573</td>
<td>2.96 ± 0.42</td>
<td>2.25 ± 0.61</td>
<td>37.7 ± 1.9</td>
<td>33.2 ± 2.6</td>
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<tr>
<td>Group</td>
<td>5.03 ± 0.54</td>
<td>2.50 ± 0.98</td>
<td>39.4 ± 0.5</td>
<td>30.8 ± 4.6</td>
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</tr>
</thead>
<tbody>
<tr>
<td>675</td>
<td>3.62 ± 0.98</td>
<td>0.60 ± 0.36</td>
<td>40.0 ± 0</td>
<td>19.3 ± 10.7</td>
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<tr>
<td>872</td>
<td>2.88 ± 0.47</td>
<td>0.67 ± 0.35</td>
<td>40.0 ± 0</td>
<td>18.5 ± 0.6</td>
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<td>522</td>
<td>2.57 ± 0.41</td>
<td>0.29 ± 0.15</td>
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<td>13.3 ± 6.5</td>
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<tr>
<td>Group</td>
<td>3.02 ± 0.62</td>
<td>0.52 ± 0.28</td>
<td>40.0 ± 0</td>
<td>17.1 ± 5.9</td>
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**TABLE 1**

Mean individual and group control rates of responding (resp/sec; RR) and numbers of reinforcer deliveries (Del) under each component of a mult FR30 food (Fd), FR30 cocaine (Coc) schedule, taken from 4–9 intervening control sessions when effects of phentermine were assessed (± S.D.)

Three unit doses (10, 30, or 100 μg/kg) of cocaine were studied.
component was decreased compared with those at lower unit doses. This was due both to a decrease with monkey no. 872 and because the three monkeys with the lowest rates of responding were studied in this condition. At this unit dose, all food deliveries were obtained. At 100 μg/kg/injection, rates of cocaine-maintained responding were decreased compared with those maintained by lower unit doses in the same monkeys, and the number of cocaine deliveries was decreased about 50% (see Fig. 3).

Figure 1 shows the mean effects of phentermine on responding maintained by food and three different unit doses of cocaine (10, 30, and 100 μg/kg/injection). In general, phentermine had little effect on food-maintained responding, although there was one exception: for monkey no. 573, rates of food-maintained responding were decreased by 1 mg/kg (at 10 μg/kg/injection) and 3 mg/kg (at all three unit doses) phentermine. Low doses (0.3–0.56 mg/kg) of phentermine had little effect on food-maintained responding, although there was one exception: for monkey no. 573, doses of phentermine greater than 0.56 mg/kg generally decreased cocaine-maintained responding in a dose-dependent manner. With the exception of monkey no. 573, doses of phentermine greater than 0.56 mg/kg always decreased cocaine-maintained responding to a greater extent than food-maintained responding. Table 2 shows that phentermine dose-dependently decreased the number of cocaine deliveries at doses that generally had little or no effect on the number of food deliveries. The decrease in the number of food deliveries with 1.7 and 3 mg/kg of phentermine at 30 μg/kg/injection cocaine was due solely to monkey no. 573.

The total number of food deliveries was equally distributed over all four components of the session for all unit doses of cocaine and treatment doses of phentermine (data not shown). Table 2 shows that the distribution of cocaine deliveries over the session varied with the unit dose of cocaine. When the unit dose was 10 μg/kg/injection, almost all available cocaine deliveries were obtained in each of the four cocaine components during control sessions. Phentermine generally had little effect on the distribution of cocaine deliveries over the session, with two exceptions. With 1 mg/kg phentermine cocaine deliveries decreased over the session. With 5.6 mg/kg phentermine (the highest dose studied) cocaine deliveries only occurred in the first component of the session. When 30 μg/kg/injection cocaine-maintained responding, the number of cocaine deliveries decreased over successive components of the session. Phentermine had little effect on this trend except that, with 3 mg/kg, the trend was not apparent, and with the highest dose studied (10 mg/kg), cocaine deliveries occurred only in the first component of the session. When 100 μg/kg/injection cocaine-maintained responding, there was a general decrease in the number of drug deliveries over the session, although the number of deliveries in the third component was often greater than that in the second component.

Figure 2 displays representative cumulative response records for control performances at three different unit doses of cocaine and the effects of selected doses of phentermine. These records are arranged sequentially as the first through fourth (left to right) pairs of food (left) and cocaine (right) components to occur during a session. They show that, for each unit dose of cocaine, food maintained high rates of responding that were largely unchanged over the session. They also show that, with 10 μg/kg/injection, uniform rates of cocaine-maintained responding occurred over the session, and with the two higher unit doses of cocaine, rates of cocaine-maintained responding declined over the session. These records illustrate that low doses of phentermine had little effect on the rates and patterns of responding maintained by either event and higher doses of phentermine decreased responding maintained by 10 and 30 μg/kg/injection cocaine. The record of baseline performance with 100 μg/kg/injection shows that high rates of responding initially occurred in each cocaine component, but after a few cocaine deliveries responding decreased.

Subacute Assessment. Fig. 3 shows that the effects of both acute and subacute phentermine differed across monkeys. For monkey nos. 872 and 522, the initial acute dose of

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**Fig. 1.** Acute effects of phentermine on rates of responding maintained under a mult FR 30 food (○), FR 30 cocaine (□) schedule with different unit doses (10–100 μg/kg/injection, left-right) of cocaine. Abscissa; dose of phentermine (mg/kg). Ordinate; effect, expressed as the mean (±S.E.M.) percent of individual control rates of responding (n = 3–4, see below); control variability (filled symbols) is expressed as the average of individual coefficients of variation. Monkey no. 675 was not studied at 100 μg/kg/injection (n = 3), and at this unit dose only one animal (no. 872) was given 10 mg/kg. Doses higher than 3 mg/kg phentermine were never given to no. 573 during acute studies.

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phentermine decreased cocaine-maintained responding completely with little or no effect on food-maintained responding. For monkey no. 675, the initial acute dose of phentermine decreased cocaine-maintained responding completely and decreased food-maintained rates of responding about 25%. Subacute 5.6 mg/kg phentermine consistently decreased cocaine-maintained responding but had different effects on food-maintained responding in each of these animals. This subacute dose had no effect in monkey no. 522, and decreased rates of responding in monkeys no. 675 and 872. Lowering the subacute dose of phentermine to 3 mg/kg sustained the decrease in rates of cocaine-maintained responding previously observed with 5.6 mg/kg in these three monkeys. With subacute 3 mg/kg phentermine, rates of food-maintained responding were either unaffected (no. 522), similar to those seen with 5.6 mg/kg in these three monkeys. With 1 mg/kg phentermine, rates of food-maintained responding increased to about 2.66 resp/sec. When 3 mg/kg was given before the next session, phentermine had little effect on rates of responding during the food component but decreased rates of responding in the cocaine component. Rates of responding in both components continued to decline on days when phentermine was not given. On subsequent occasions, lower doses of phentermine increased rates of food-maintained responding, although these increases never exceeded the rate of food-maintained responding previously observed at 10 µg/kg/injection. Phentermine only decreased responding in the cocaine component. Phentermine had no effect on the number of cocaine-maintained responding increased. When the acute effects of 5.6 mg/kg phentermine were redetermined, both food and cocaine-maintained responding were almost completely decreased.

For each animal (except monkey no. 573), acute 5.6 mg/kg phentermine had little effect on the number of food deliveries; excluding the second and third session for monkey no. 675, the number of food deliveries with subacute 5.6 mg/kg phentermine averaged 38.3 per session. During the subacute 3 mg/kg phentermine, the number of food deliveries per session averaged 39.8 (including monkey no. 573). During the subacute saline, the number of food deliveries was always 40.

**Low Unit-Dose Assessment.** Fig. 4 (top) shows that before decreasing the unit dose of cocaine, 10 µg/kg/injection sustained high mean rates of food (2.92 resp/sec) and cocaine (3.05 resp/sec) maintained responding. This figure also shows that, when the unit dose of cocaine was decreased to 1 µg/kg/injection, rates of responding in the cocaine component decreased over the first three sessions to about 1.23 resp/sec, and rates of responding during the food component also decreased to about 2.66 resp/sec. When 3 mg/kg was given before the next session, phentermine had little effect on rates of responding in the food component but decreased rates of responding in the cocaine component. Rates of responding in both components continued to decline on days when phentermine was not given. On subsequent occasions, lower doses of phentermine increased rates of food-maintained responding, although these increases never exceeded the rate of food-maintained responding previously observed at 10 µg/kg/injection. Phentermine only decreased responding in the cocaine component. Phentermine had no effect on the number of cocaine-maintained responding increased.
of food deliveries and decreased the number of cocaine deliveries (data not shown).

When cocaine-maintained responding was re-established (or initially, for no. 522) with 10 μg/kg/injection, mean rates of both cocaine- (2.02 resp/sec) and food- (1.92 resp/sec), maintained responding were lower than those seen in the first experiment. This was partially due to the low food rates for no. 522, and partially to a decrease in rates for no. 31 (see Fig. 2. Representative cumulative response records showing performances maintained under the mult FR 30 food, FR 30 cocaine schedule at three different unit doses of cocaine and for the effects of phentermine on food- and cocaine-maintained (10 and 30 μg/kg/injection only) responding. Sessions consisted of four cycles (left-to-right) of an FR30 food component (left record of each row) and an FR30 cocaine (right record) component; responding during between-component TOs has been excised to conserve space. The recorder ran continuously during a session. Horizontal portions of the record indicate when responding did not occur. The pen stepped up with each response and reset after completion of a component. Short vertical deflections on the record indicate reinforcer deliveries. Abscissa: time. Ordinate: cumulative responses.
When both the food component was eliminated and the unit dose was decreased to 1 \( \mu g/kg/injection \), rates of responding in the cocaine component decreased over the subsequent six sessions. When 1 \( mg/kg \) phentermine was given before the eighth session, mean rates of responding decreased compared with the preceding session. This effect occurred for all animals except no. 31. Mean rates of responding on the session following 1 \( mg/kg \) phentermine were increased compared with the session preceding phentermine in all animals. However, mean rates of responding during the next (tenth) session with 1 \( \mu g/kg/injection \) were increased more than those of the ninth session, an effect primarily due to increased rates in two monkeys (no. 522 and no. 72). When 1 \( mg/kg \) phentermine was given on the eleventh session of exposure to a unit dose of 1 \( mg/kg/injection \), mean rates of responding were decreased compared with all preceding days.

Assessment on GBR 12909-Maintained Responding. Under the mult FR 30 food, FR 30 GBR 12909 schedule, food-maintained high rates of responding (see Fig. 5) and all food deliveries were obtained for three of the four monkeys. One monkey (no. 450) never responded in the fourth food component, resulting in 30 food deliveries per session and lower rates of responding in the food component. GBR 12909 maintained high rates of responding (see the legend of Fig. 5) and under baseline conditions almost all GBR 12909 deliveries were obtained (range = 39.6 ± 0.9–37.6 ± 1.7).

Figure 5 shows that phentermine had different effects on responding maintained by food and GBR 12909 in each monkey. For one monkey (no. 561), phentermine had no effect on food-maintained responding. For another (no. 941), phentermine decreased GBR 12909-maintained responding at doses lower than the doses that decreased food-maintained responding. For a third monkey (no. 450), phentermine decreased food-maintained responding at lower doses than those that decreased GBR 12909-maintained responding. For the fourth monkey (no. 769), phentermine decreased both food- and GBR 12909-maintained responding over a similar
range of doses. In general, the effects of phentermine on reinforcer deliveries were similar to those seen on rates of responding (data not shown).

**Discussion**

Phentermine decreased cocaine-maintained responding in the current study. Earlier reports showed that methamphetamine decreased methamphetamine-maintained responding (Pickens et al., 1968), and d-amphetamine or phenmetrazine decreased cocaine-maintained responding (Wilson and Schuster, 1973). Together, these studies suggested that drug self-administration could be decreased by drugs that have pharmacological effects similar to those of the reinforcer. However, the behavioral specificity of those results was not established in the previous studies. The current study shows that phentermine could decrease cocaine-maintained responding at doses that do not decrease food-maintained responding in the same animal during the same session. These findings are similar to those of recent studies showing that GBR 12909 (Glowa et al., 1995a, b), CFT (Glowa and Wojnicki, 1996), and cocaine (Glowa and Fantegrossi, 1997) decrease cocaine-maintained responding at doses that have less of an effect on food-maintained responding. These results are important because they clearly show that cocaine-maintained responding can be affected by doses of drugs less than those that have nonspecific effects. They also add to a growing literature showing that drugs can affect responding maintained by drug and food differently. However, the current study also raises several issues with respect to interpreting those differences.

The current study does not support the possibility that cocaine-maintained responding is decreased because phentermine affects the potency of cocaine. There is no evidence of a rightward shift in the unit dose-effect function for cocaine, as responding maintained by unit doses from 10 to 100 μg/kg injection is affected by phentermine in a similar manner. Phenmetamine does not generally increase low rates of responding associated with a low unit dose (1 μg/kg injection) of cocaine, consistent with earlier reports showing that GBR 12909 (Glowa et al., 1995a) and CFT (Glowa and Wojnicki, 1996) do not increase responding associated with a low unit dose of cocaine in the monkey. These data suggest that phentermine does not shift the unit dose-effect function for cocaine to the left. In contrast, because the D₃ agonist 7-OH-DPAT increases responding associated with low doses of cocaine in the rat (Caine and Koob, 1995), some drugs may produce a leftward shift. The differences between these effects raise questions as to whether drug-induced increases in responding associated with low doses of cocaine are species-specific, occur with only certain types of DA agonists, or are unrelated to the reinforcing effects of cocaine.

A distinctive feature of many drugs that selectively decrease cocaine-maintained responding is that they support self-administration under other conditions. The possibility has been raised that treatment of drug self-administration with an agent that has pharmacological effects similar to those of the self-administered drug may result in a satiation-like effect (Wilson and Schuster, 1973). A related possibility is that response-independent drug treatment substitutes for response-dependent drug delivery. Substitution is a functional relationship between reinforcers that is inferred when
a change in the cost (responses/unit dose) for one reinforcer results in a change in the consumption of another reinforcer (Hursh, 1993). Decreases in drug-maintained responding have been well documented in studies where concurrent access to alternative reinforcers has been arranged (Carroll et al., 1989; Nader and Woolverton, 1991). Response-independent delivery of a potentially reinforcing event may have effects on responding similar to those of alternative reinforcement. Rachlin and Baum (1972) maintained responding under concurrent variable-interval schedules of food delivery, varying several reinforcement parameters. As expected, when the relative magnitude or frequency of food delivery was increased in one component, responding in the alternate component decreased. A similar effect was observed in the alternate component when response-independent food was delivered in the other component. Response-independent delivery of phentermine may represent a situation in which the minimal cost (i.e., free) of drug delivery decreases consumption of a more expensive alternative commodity (i.e., cocaine). This interpretation is consistent with the results of Wurster et al. (1977), in which treatment with methadone decreased choice for heroin while increasing choice for food. However, as few studies have directly addressed whether more direct measures of the reinforcing effects of drugs are decreased by drug treatment, these conclusions remain speculative.

Previous studies have noted that GBR 12909 (Glowa et al., 1995a), 7-OH-DPAT (Caine and Koob, 1995), and cocaine (Glowa and Fantegrossi, 1997) decrease responding maintained by lower unit doses of cocaine more than responding maintained by higher unit doses of cocaine. Other studies have shown that drugs decrease responding maintained by lower densities of food delivery more than responding maintained by higher densities of food delivery (Egli et al., 1992). These differences in the effects of drug on responding maintained by the same event may occur because responding maintained under conditions that engender more effective reinforcement is more resistant to change than responding maintained under conditions engendering less effective reinforcement (Nevin, 1974). It has been argued that higher unit doses of cocaine are more effective reinforcers based on the results of choice (Johanson and Schuster, 1975), progressive-ratio (Roberts and Richardson, 1992), and response acquisition (Schenk et al., 1991) procedures. In the current research, however, phentermine decreased responding maintained by
all three unit doses of cocaine in a similar manner. These effects are inconsistent with a resistance-to-change explanation of the selective decreases in cocaine-maintained responding by drug treatment. Other studies have also failed to find that reinforcement variables determine differences in drug effects. For example, Cohen (1986) reported little difference in the effects of several drugs on responding maintained under random-interval schedules of food presentation that arranged different densities of reinforcement. Currently, factors responsible for differences in the effects of phentermine and other drugs such as GBR 12909 on responding maintained by different unit doses of cocaine are not known.

Phentermine also decreased responding maintained by GBR 12909, in some cases at doses similar to those that decreased food-maintained responding. For two monkeys, food maintained higher rates of responding than GBR 12909, and higher doses of phentermine were required to decrease food-maintained responding. For monkey no. 769, both events maintained similar rates of responding, and phentermine had similar effects on both performances. For monkey no. 450, GBR 12909 maintained higher rates of responding than those maintained by food, and higher doses of phentermine were required to decrease GBR 12909-maintained responding. These data suggest that the rate-decreasing effects of phentermine were influenced by control rates of responding. Although rate of responding is not a direct measurement of the reinforcing effects of an event, under FR schedules it may reflect certain features of the maintaining event. For example, Powell (1969) found that magnitude of reinforcement was positively related to rate of responding under FR schedules of food presentation. As the current studies did not specifically isolate similar determinants of phentermine's effects, it remains possible that, under different circumstances, selective decreases in food-maintained responding could be obtained. Identifying determinants of the selectivity of drug effects on cocaine-maintained responding will be relevant to understanding the significance of drug-induced decreases in drug-maintained responding.

The current results suggest that a DA releaser can produce behavioral effects similar to those obtained with drugs that block DA reuptake sites (e.g., GBR 12909, CFT, cocaine). While these results may suggest that occupation of a reuptake site is not required to decrease cocaine-maintained responding, other DA releasers (e.g., d-amphetamine) have been shown to interact with the uptake site (Meiergerd and Schenk, 1994). Some pharmacological actions of phentermine differ from those of d-amphetamine. The additional α-methyl group of phentermine attenuates its central stimulant and cardiovascular effects as compared with amphetamine (Biel, 1970). Phentermine is eliminated (T1/2) at a slower rate, and the amount of drug excreted unchanged is higher than that of amphetamine (Beregi et al., 1970). Phentermine (Rothman et al., 1996), as well as GBR 12909, (Baumann et al., 1994) attenuate the rise in extracellular DA in the nucleus accumbens produced by cocaine injections. Increases in extracellular DA have been associated with the abuse potential of drugs (Di Chiara and Imperato, 1988). The fact that both GBR 12909 and phentermine can attenuate two different preclinical measures associated with the abuse potential of cocaine, the rise in extracellular DA induced by cocaine and the self-administration of cocaine, seems to provide convergent data pertaining to their ability to modify the neurobehavioral effects of cocaine.

The sustained difference in effect of phentermine on food- and cocaine-maintained responding under most of the subacute treatment conditions provided additional data showing that phentermine could affect those two behaviors differently. One monkey (no. 573) in these studies illustrated that individual differences in drug effects occur with phentermine. For this monkey, relatively low acute doses (1 mg/kg) of phentermine decreased food-maintained responding when the unit dose was 10 μg/kg/injection, and higher doses (3 mg/kg) decreased responding maintained by both events to a comparable extent. However, acute doses of 1 and 1.7 mg/kg phentermine decreased responding maintained by 30 μg/kg/injection cocaine, and the subacute dose of 3 mg/kg phentermine decreased responding maintained by 10 μg/kg/injection cocaine to a greater extent than food-maintained responding in this monkey. Thus, while this monkey appeared to be more sensitive to the rate-decreasing effects of phentermine in general, in each experiment at least one dose of phentermine decreased responding maintained by cocaine to a greater extent than food-maintained responding. Thus, phentermine produced selective effects in every monkey.

In summary, the current findings are important for several reasons. They link recent observations that phentermine can decrease cocaine intake in humans to decreases in cocaine-maintained responding in animals. This observation could help validate the use of self-administration studies to identify effective pharmacotherapies for drug abuse (Mello and Negus, 1996). Because phentermine may exert effects through mechanisms distinct from those of DA reuptake inhibitors, the range of drugs observed to produce selective decreases on cocaine self-administration was extended by this study. The apparent efficacy of phentermine in selectively decreasing responding maintained by relatively high unit doses of cocaine may be particularly interesting with respect to its potential as a treatment for cocaine abuse in humans and for interpreting drug-induced decreases in drug-maintained responding. Further research is needed to identify factors that contribute to individual differences in the effects of drugs on responding maintained by cocaine and the extent to which drug treatment modifies the reinforcing effects of cocaine.

References
