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Discriminative Stimulus Effects of Dopaminergic Agents in Rhesus Monkeys

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KOETZNER, L., A. L. RILEY AND J. R. GLOWA. *Discriminative stimulus effects of dopaminergic agents in rhesus monkeys.* PHARMACOL BIOCHEM BEHAV **54**(2) 517-523, 1996. — Recent reports have shown that treatment with dopamine reuptake inhibitors can selectively decrease responding maintained by low doses of cocaine in rhesus monkeys. This may occur because response-independent delivery of a reuptake inhibitor and response-dependent cocaine have common effects. One behavioral effect that dopamine reuptake inhibitors and cocaine share is their ability to serve as a discriminative stimulus. To compare discriminative effects of several dopaminergic agents with their ability to attenuate cocaine-maintained responding, three rhesus monkeys were first trained to discriminate intravenous injections of cocaine (0.1 mg/kg) from saline. Following generalization testing with various doses of cocaine (0.001-1.0 mg/kg), the relative potencies of phentermine (0.03-1.0 mg/kg), *d*-amphetamine (0.01-1.0 mg/kg), GBR 12909 (0.01-1.0 mg/kg), and buspirone (0.03-0.56 mg/kg) to substitute for cocaine were assessed. Each drug except buspirone resulted in predominantly cocaine-appropriate responding at doses that were generally without rate-decreasing effect. The ED_{50} for the ability of these drugs to substitute for cocaine exhibited the same rank order as that for their effectiveness in decreasing cocaine-maintained responding. Thus, the current results show that the potencies of dopaminergic drugs to decrease cocaine-maintained responding and substitute for cocaine in a drug discrimination paradigm are related.

Phentermine *d*-Amphetamine GBR 12909 Cocaine Drug abuse Drug discrimination Rhesus monkeys

COCAINE abuse is a nationwide epidemic (15) for which therapeutic intervention is sorely needed. The benefits of a pharmacological treatment (e.g., low cost, ease of administration) make medications an attractive form of treatment. However, there is little agreement on the exact basis or success of the pharmacological approach (16). Recent reviews have emphasized that with increased understanding of the mechanisms of cocaine's effects, more effective treatments may be possible (26). The finding that a dopamine (DA) uptake site is strongly associated with cocaine-maintained behavior (24) suggests that compounds directed at that site may be effective therapeutics. Concordant with this possibility, clinical researchers have reported moderate success with DA receptor agonists (7,12). More recently, Rothman (25) has suggested the use of high-affinity DA uptake inhibitors (29) as potential treatment drugs. Such drugs might decrease cocaine binding, or simply diminish the effect of cocaine on synaptic DA concentrations (27). The DAergic selectivity of reuptake inhibitors such as GBR 12909 may also minimize side-effects, as these agent affect serotonin and norepinephrine uptake and sodium channel blockade less than other DA reuptake inhibitors (1).

The possibility that GBR 12909 can decrease cocaine's biochemical effects has prompted studies to test whether GBR 12909 could modify the behavioral effects of cocaine. Pretreatment with GBR 12909 has been shown to selectively decrease cocaine-maintained responding in rhesus monkeys, at doses that have no effect on food-maintained responding (8,9). Similar results have been obtained for the weak DA releaser phentermine (10), a drug that has been used to treat obesity (13) and more recently has been suggested as a medication for cocaine and alcohol abuse (12). Interestingly, when high unit doses of cocaine are self-administered, this selective behavioral decrease in cocaine- (as opposed to food-) maintained responding has also been observed (8), allowing for the possibility that cocaine intake is self-regulated (i.e., a satiation effect results in decreased responding). One way in which

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DAergic drugs may attenuate cocaine self-administration is by producing effects similar to those of high unit doses of cocaine. While no studies have directly related a mechanism of action to this type of behavioral effect, drug discrimination techniques have previously served as a method to study behavioral change thought to be mediated by similar neurochemical events (3,21). For example, if GBR 12909 reduces cocaine self-administration through a process that involves a neurochemical effect similar to that produced by cocaine, then it may substitute for cocaine in a drug discrimination paradigm. Results from previous drug discrimination studies suggest that cocaine and GBR 12909 share discriminative effects (17,20). For example, rhesus monkeys trained to discriminate cocaine from saline respond in a cocaine-appropriate manner after GBR 12909 is administered (17). Likewise, squirrel monkeys trained to discriminate GBR 12909 from saline emit GBR-appropriate responses after cocaine is administered (20). However, these studies do not allow direct comparisons between the effects of drugs that generalize to cocaine and those that reduce cocaine self-administration. For example, Melia and Spealman (20) studied GBR 12909 as a training drug in a drug discrimination study. While Kleven, Anthony, and Woolverton (17) studied cocaine as a training drug, high doses (above amounts usually self-administered in a session) were employed, with a relatively long delay between drug infusion and the beginning of the test session. Thus, a variety of procedural differences complicate such comparisons.

In order to more directly compare the discriminative effects of cocaine-like drugs with their abilities to attenuate cocaine self-administration, a drug discrimination study was designed to closely parallel previous studies of drug effects on cocaine self-administration (8,9). Rhesus monkeys were trained to discriminate cocaine and vehicle infusions. Probe sessions were then conducted following administration of different doses of cocaine or other drugs. GBR 12909 and phentermine were tested in probe sessions. In addition, *d*-amphetamine was tested because it is known to share cocaine's discriminative effects (17) and attenuate cocaine self-administration (9), even though it is unlikely it would ever be used as a pharmacotherapeutic drug to treat cocaine abuse. The anxiolytic buspirone was tested as a negative control drug that was not expected to share cocaine's discriminative effects (23).

METHODS

Subjects

Subjects were three adult male rhesus monkeys (*Macaca mulatta*) weighing between 4.5 and 9 kg when maintained at 90% of their free-feeding weights. Water was continuously available in both the home cages and test chambers. Subjects were housed in individual stainless steel cages. Prior to drug training, subjects were prepared with a catheter, surgically inserted in either the left or the right exterior jugular vein. The catheter was attached to a SC infusion port (Access Technologies), located on the back of the monkey, between the scapulae [for details, see (30)]. The monkeys were trained to exit the home cage and sit in a standard primate chair (Primate Products), initially for weighing and to receive drugs, and later for discrimination testing.

Apparatus

Initial training was conducted in the home cage, with intelligence panel boxes hung in the open door of the chamber during testing. The side of the box facing the monkey (intelligence panel) was 60 cm high × 30 cm wide. Within the box, three pairs of lights were arranged in a line 20 cm below the top of the panel. Two response levers were placed 10 cm above the bottom of the panel, one on either side. A feedback relay located in the box was triggered by lever presses during the session. A feeder was positioned in the box so that food pellets dropped into the food cup mounted on each monkey's home cage. Animals were weighed in the restraint chair before each session, infused with a saline or cocaine solution, and then returned to the home cage for the session.

Later, experimental sessions were conducted in individual test chambers, each designed to accommodate a primate chair. Each of these chambers, constructed from cinder blocks and laminated fiberboard, was fitted with a 45 W fluorescent light and fan mounted on the door behind the chair and syringe drivers on the roof of the chamber. A 45 × 60 cm aluminum intelligence panel was mounted on the far inside wall of the chamber facing the monkey. A pair of response levers modified to use 0.5 cm thick aluminum bars as paddles were set 4″ from the bottom of the panel, separated by about 18″ (to correspond to the arm restraints of a primate chair). A series of six lights was mounted in a line 4″ from the top of the panel; these lights were lit whenever food could be produced by responding. A food cup for pellet delivery was mounted in the center of the panel; a water spigot was mounted slightly above the cup and to one side. White noise was supplied through speakers installed in each chamber. Recording and control of contingencies were programmed by a computer system (MED Associates). The computer also controlled one cumulative recorder (Gerbrands) per chamber, which produced records of each individual session. Drug infusions were conducted in the chamber, delivered through an infusion line attached to a syringe driver (Razel).

Drugs

Cocaine hydrochloride (National Institute on Drug Abuse) was dissolved in physiological saline to obtain a concentration of 0.15 mg/ml. GBR 12909 dihydrochloride (Laboratory of Medicinal Chemistry, National Institutes of Health) was dissolved in distilled water with lactic acid as necessary and then diluted with saline to concentrations of 0.3 and 1.0 mg/ml. Phentermine hydrochloride and *d*-amphetamine hydrochloride (Sigma) and buspirone hydrochloride (Bristol-Myers) were dissolved in saline at a concentration of 1.0 mg/ml (0.3 mg/ml for later test sessions with *d*-amphetamine). All infusions were delivered at a rate of 0.3 ml/s. Duration was used to control infusion volume.

Procedure

Early training took place using intelligence panels that were attached to the home cage. Magazine and lever-press training was accomplished by simply filling the food cup with pellets and after all the pellets were gone, arranging a continuous reinforcement schedule for both levers. After reliable responding was established, the response requirement on each lever was gradually increased until responding was reliably maintained under a fixed-ratio 30 schedule (FR30). During subsequent sessions, 25 pellets could be produced by responding on either lever. When rates of responding appeared to reach asymptote and the numbers of responses on each lever were approximately equal, drug discrimination training began.

At the beginning of daily training sessions, each monkey was removed from the home cage, brought to a procedure room, and infused with 2 ml of saline to clear the catheter.

Then 2 ml/kg of either a cocaine solution or its vehicle was infused (0.3 mg/kg). A 2 ml (postdrug) saline flush was then delivered, the monkey was returned to his cage, and the test apparatus was placed on the cage. Five minutes after the infusion was completed, the test session started and the lights on the intelligence panel were illuminated. For each monkey, one lever was designated the drug-appropriate lever and one the saline-appropriate lever. Assignment of the drug lever (i.e., right or left lever) was made in a semi-balanced manner with respect to initial lever preference. After a drug infusion, 50 food pellets could be earned on the drug lever; responses on the saline lever were recorded but had no programmed consequences. After a saline infusion, contingencies associated with the two levers were reversed. After the behavioral component began (i.e., 5 min after the infusion ended), the lights remained lit until the monkey completed all of the fixed ratio requirements for the component. Then, the apparatus was removed.

In order to hasten the acquisition of the discrimination, the training protocol was subsequently modified to a four-component session, suitable for utilizing a cumulative dosing procedure. The number of food deliveries was reduced from a total of 50 to 10 per component, and the time between the end of the infusion and the beginning of the component was reduced to 1 min. Fifteen minutes after the component began, the infusion for a second component began. Four components composed one test session. A postinfusion saline flush (2 ml) was administered after the fourth infusion. Drug and vehicle treatments were semirandomly assigned when baseline performances were stable; if cocaine was administered, all subsequent components that day followed cocaine infusions. To avoid an invariant relationship between component number and treatment, some sessions were run with four vehicle or four cocaine infusions. For this phase of the experiment, test sessions were switched to the cinder block chambers and the cocaine dose was reduced to 0.1 mg/kg. Accuracy of drug lever selection became asymptotic, but because it did not seem that the discrimination had been acquired (i.e., responses were not distributed according to drug treatment), a more stringent protocol was put into place.

Under the more stringent training protocol, the component was terminated when the total number of responses emitted was equal to the minimum number of responses required to earn all of the food pellets available in the component. As a result, inappropriate responding served to reduce the amount of food available. The first response on a lever reset the ratio requirement on the other lever to 30. Finally, each completed ratio on the inappropriate lever resulted in a 10-s time out, during which both levers were disabled (i.e., responses were not counted) and the cue lights were turned off. Subjects were considered to have met the criterion (i.e., acquired the discrimination) if their drug lever selections during the first ratio were above an average of 85% during drug training sessions and below an average of 15% during vehicle training sessions averaged for 4 days (i.e., more than 85% infusion-appropriate responding for 4 days).

Probe sessions were identical to training sessions except for the drug solution used and that 30 consecutive responses on either lever produced a food pellet regardless of drug treatment. These sessions were also conducted in four components; each probe session followed two or more regular training sessions, provided that the subject showed at least 85% infusion-appropriate behavior. For training sessions, 2 ml/kg cocaine or saline was delivered before each component. For probe sessions, 0.03 ml/kg of the solution to be tested was delivered before the first component, 0.1 ml/kg before the second, 0.3 ml/kg before the third, and 1.0 ml/kg before the final component. Components of probe sessions continued until 300 responses were emitted or 15 min elapsed, but only the behavior emitted before the delivery of the first food pellet in each component was analyzed. ED_{50} values (i.e., the dose at which 50% drug-appropriate responding occurred) were derived from logistic regressions (6) by computer. Regressions were first obtained by fitting a logistic equation with four parameters (minimum effect, or the lowest proportion of drug-appropriate responding; maximum effect, or the highest proportion of drug appropriate responding; ED_{50}; and a slope parameter). If the variability in the data accounted for by the model was less than 85% (i.e., $r^2 < 0.85$, which was true for the data for one drug treatment in each of two subjects), regressions were recalculated by fitting an equation with the minimum and maximum effects set at 0 and 100%, respectively.

RESULTS

Responding during the training components that immediately preceded the probe sessions was distributed between levers in a treatment-appropriate manner. Cocaine and saline infusions were followed by 90.4 and 1.7%, 92.1 and 6.6%, and 99.2 and 3.8% drug-appropriate responding for subjects J927, 5992, and 5993, respectively. Response rates during training sessions were proportionately similar for drug and vehicle components for one subject (5993: cocaine, 3.47 responses per second (r/s); saline, 4.41 r/s), higher after drug infusions for another (5992: cocaine, 3.71 r/s; saline, 2.01 r/s) and higher after saline infusions for the third (J927: cocaine, 0.27 r/s; saline, 1.13 r/s).

Cocaine infusions during probe sessions elicited drug-appropriate responding in a dose-dependent manner (see Figs. 1–3). The proportion of drug lever responses during probe sessions approximated or exceeded that observed during drug training components (100%, subjects 5993 and J927; 90.9%, subject 5992). The lowest dose at which cocaine occasioned 95% drug-appropriate responding was substantially below the training dose for one subject (5993: 0.01 vs. 0.1 mg/kg) and above the training dose for another (J927, 0.3 vs. 0.1 mg/kg); the greatest proportion of cocaine-appropriate responding for subject 5992 was at the training dose. Response rates remained between the mean values from training components for all doses tested in one subject (5993) and exceeded the training values slightly at low to medium doses in the other two subjects (J927: 1.51 vs. 1.13 r/s; 5992: 4.16 r/s vs. 3.71 r/s; in training vs. test sessions, respectively).

Using 85% cocaine-appropriate responding as a criterion for substitution for cocaine, GBR 12909 substituted for cocaine in two subjects (5992: 94.1–100%; 5993: 92.8% cocaine-lever responding) and produced some cocaine-appropriate responding in the third (J927: 62.7% at 1 mg/kg); see Figs. 1–3. The highest dose to be tested on J927 did not disrupt performance (response rates were not decreased). However, higher doses were associated with large decreases in response rates and might have disrupted the discrimination. The lowest dose to substitute in the other subjects did not reduce response rates below control values. Phentermine substituted for cocaine at doses that did not disrupt response rate in two subjects (J927 and 5993). In the third subject (5992), the highest dose of phentermine substituted but decreased response rate to 0.16 r/s. *d*-Amphetamine substituted in all subjects, decreasing response rate slightly in one subject.

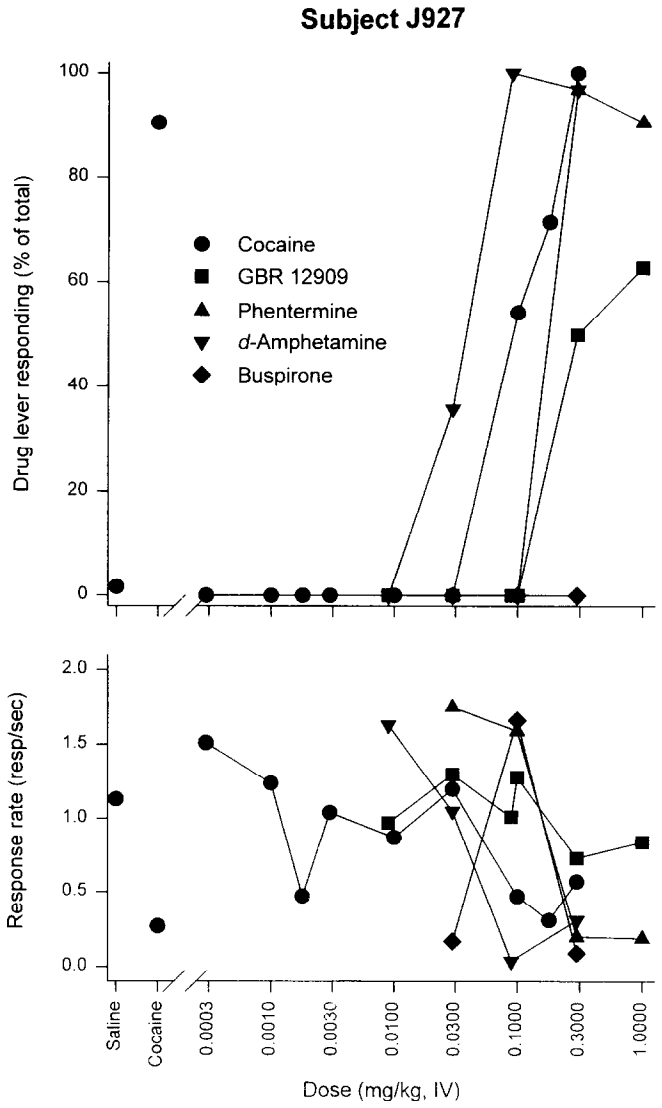

FIG. 1. Dose-response data for subject J927. The upper panel shows the proportion of drug lever responding following various IV doses of cocaine, GBR 12909, phentermine, *d*-amphetamine, and buspirone (see legend); the lower panel shows the rate of responding as a function of dose for the same drugs. Points above the saline and cocaine on the abscissa represent the average of the two training sessions that preceded each test session.

No dose of buspirone tested in this experiment produced more than 3.6% drug-appropriate responding (see Figs. 1-3). High doses (0.3 mg/kg and above) were associated with dramatic decreases in response rate; several probe components at these doses elapsed with no responses emitted at all (data not shown).

DISCUSSION

The discrimination between cocaine and its vehicle was well maintained during this study. Administration of increasing doses of cocaine resulted in the dose-dependent selection of the cocaine-appropriate lever. The complete substitution with GBR 12909 seen in two subjects concurs with previous studies indicating that GBR 12909 substitutes for intramuscular cocaine in the rhesus monkey (17) and that cocaine substitutes for intravenous GBR 12909 in the squirrel monkey (20). The relative ED_{50}s for cocaine and GBR 12909 are also consistent with these reports (i.e., cocaine is more potent than GBR 12909 for the production of cocaine-lever responding). The inability of GBR 12909 to fully substitute in one subject (J927) occurred at doses that failed to disrupt response rate, suggesting that the dose may not have been sufficiently high to substitute for the training dose of cocaine. However, a higher dose administered to another subject had been followed by a syndrome of behavioral toxicity including undirected aggressive behavior, ataxia, and mild hyperactivity. As a result, these doses were not tested in subject J927. Phentermine clearly substituted in all three subjects (although it decreased response

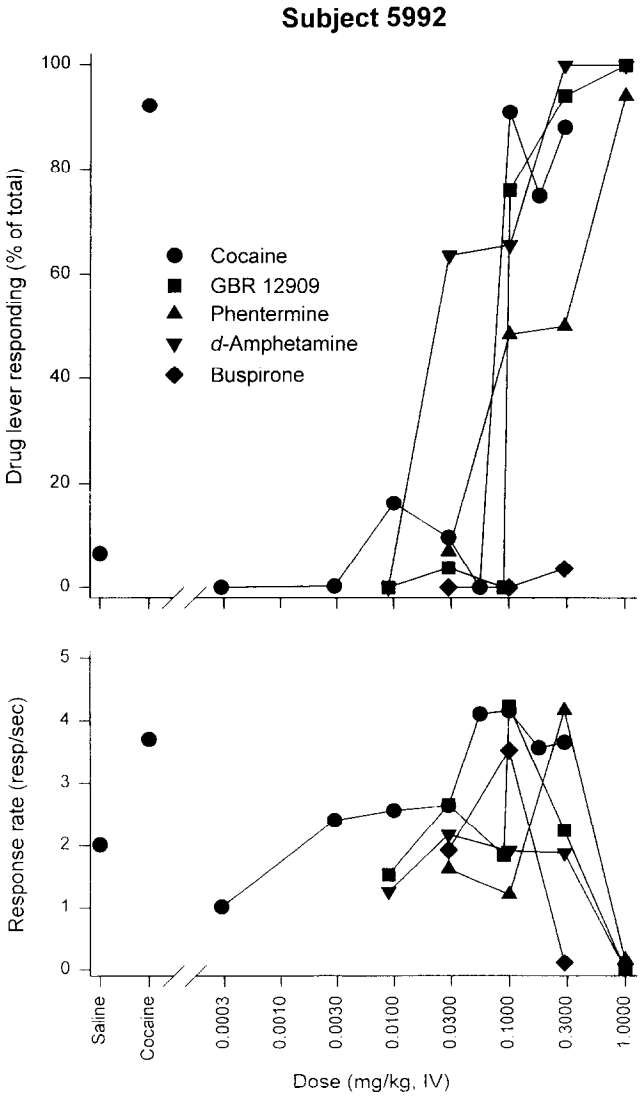

FIG. 2. Dose-response data for subject 5992. Details are as in Fig. 1.

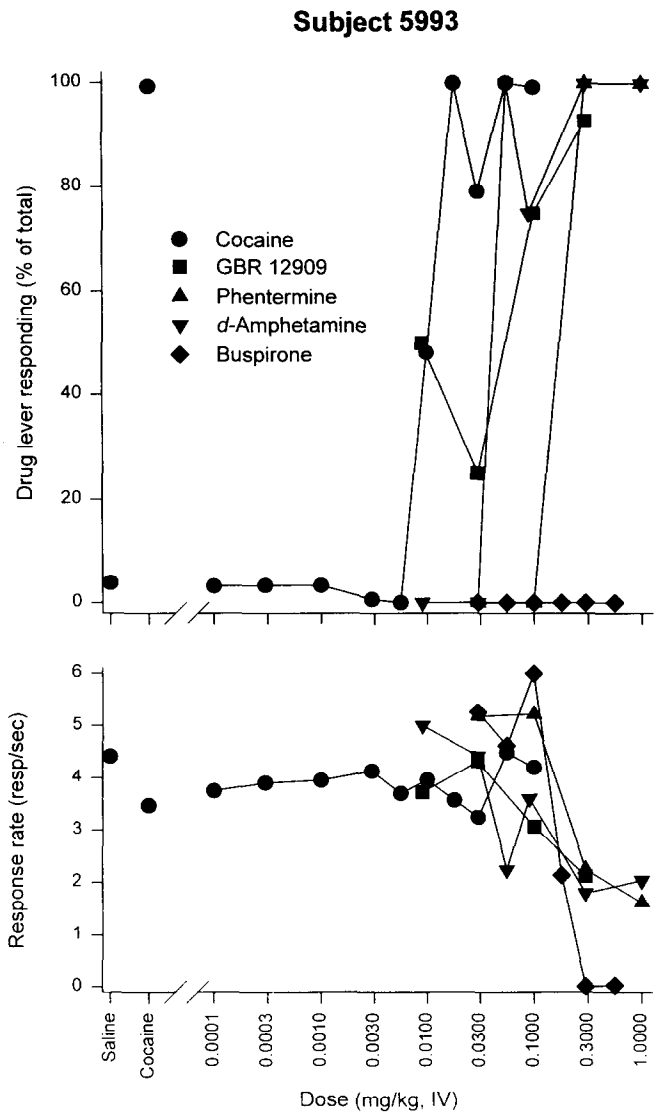

FIG. 3. Dose-response data for subject 5993. Details are as in Fig. 1.

rate in one), and was slightly less potent than GBR 12909 in generalizing to cocaine. In contrast, Wood and Emmett-Oglesby (31) found that phentermine was slightly more potent than cocaine. Finally, *d*-amphetamine substituted for cocaine at lower doses than those required for any of the other drugs and without decreasing response rate, consistent with previous reports [e.g., (17)]. Thus, GBR 12909, phentermine, and *d*-amphetamine all shared discriminative effects with cocaine.

These drugs have also been assessed as potential cocaine abuse medications (8–10). When responding was maintained under multiple FR30 schedules of food- and cocaine-presentation in monkeys, GBR 12909 and phentermine were capable of abolishing cocaine-maintained responding at doses that had no effect on food-maintained responding. *d*-Amphetamine and CFT naphthalene sulfonate (WIN 35,428) also reduced cocaine-maintained responding, but only at doses that had effects on food-maintained responding (9). Figure 4 compares the potency of these drugs for decreasing cocaine-maintained responding with their potencies for producing drug-lever responding in the monkey. The rank ordering of these agents (*d*-amphetamine > cocaine > GBR 12909 > phentermine) is the same for both behavioral measures, suggesting that the two effects are related. Previous studies have described relationships between the reinforcing and discriminative effects of drugs (2,28), consistent with the notion that these two end points are related. If these results represent a direct relationship between these two effects, it would suggest that the ability of these drugs to decrease cocaine-maintained responding may be due to their ability to attenuate the reinforcing effects of cocaine by producing a satiation-like effect. Under these conditions one might simply expect a downward shift in the unit dose–effect function in the presence of effective treatment agents, if the reinforcer is losing effectiveness (8). In contrast, treatment drugs may decrease cocaine-maintained responding by shifting the cocaine dose–effect function to the left (4,19), which would not imply a loss of reinforcing efficacy but simply a change in the dose at which it is maximal. This type of additive effect has been observed when pretreatment with cocaine and GBR 12909 were studied in combination on schedule-controlled responding, resulting in a shift of the cocaine dose–effect function to the left (14). However, in our previous studies, both GBR 12909 and CFT only depressed, rather than left-shifted the cocaine dose–effect function (8,11). If response-independent delivery had the same effect as response-dependent drug delivery, this could be inter-

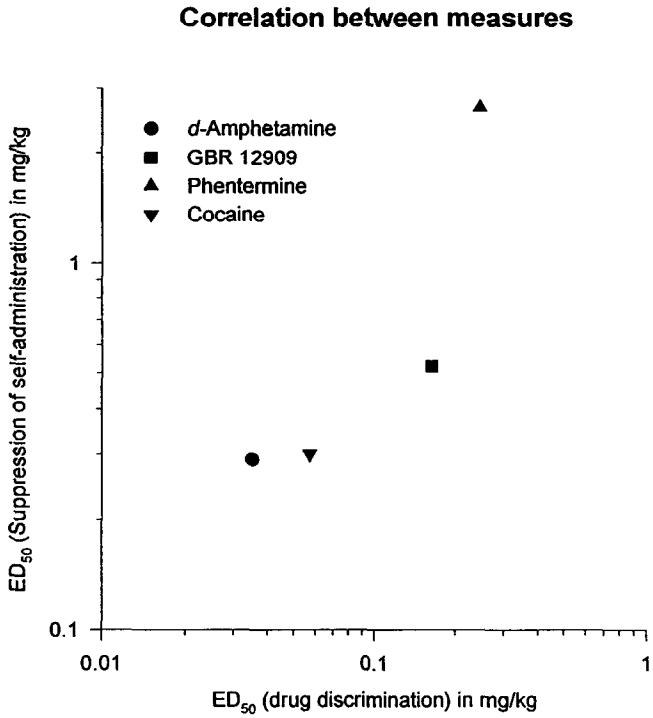

FIG. 4. Comparisons of the ED_{50} values of IV *d*-amphetamine, phentermine, GBR 12909, and cocaine to decrease self-administration [taken from (8–10)] and to substitute for cocaine (from the current drug discrimination data), under comparable conditions in rhesus monkeys.

preted as a satiation-like effect. However, another interpretation of these results is that responding maintained by low doses of cocaine is more easily disrupted by drug treatments (8). Since these psychomotor stimulants differ in their ability to decrease cocaine self-administration depending upon the dose of cocaine that maintains responding (9), it would be of interest to determine the extent to which they differ in their ability to substitute for cocaine when discriminations are established using different training doses.

The sessions conducted after administration of the 5-HT_{1A} agonist buspirone served as a procedural control and addressed serotonin's role in the cocaine discriminative stimulus. If drug-appropriate responding was elicited by anything other than cocaine-like discriminative effects (e.g., a novelty effect or syringe driver noise), buspirone treatment should have resulted in cocaine-appropriate responding; it did not. Recent studies with serotonergic manipulations have identified a role for several serotonin receptor subtypes in cocaine's effects [e.g., (3,15,19)]. These studies have used agonists and antagonists at 5-HT_1 and 5-HT_2 receptors (22) and 5-HT_3 receptors (18), finding that each subtype seems to mediate a certain amount of cocaine-like effect. Despite the involvement of these other subtypes, agonist activity at 5-HT_{1A} receptor does not appear to either attenuate (23) or reproduce (the present study) cocaine's discriminative effects.

The present study determined the dose of several agents to substitute for cocaine in a drug discrimination procedure. This dose was then compared with those previously shown to selectively decrease cocaine-maintained responding under comparable conditions. The data suggest a relationship between the potencies of the drugs to accomplish each effect, although questions remain as to the relationship between the relative efficacies of these agents on these tasks. However, the relationship is intriguing and consistent with the notion that if similarity in effect is a desired property of an agonist treatment, then drug discrimination can be effectively used to develop strategies for the treatment of drug abuse.

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