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Dopamine D_1/D_2 Antagonist Combinations as Antagonists of the Discriminative Stimulus Effects of Cocaine

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GETER-DOUGLASS, B. AND A. L. RILEY. *Dopamine D_1/D_2 antagonist combinations as antagonists of the discriminative stimulus effects of cocaine.* PHARMACOL BIOCHEM BEHAV **54**(2) 439–451, 1996. – Although data suggest that the dopaminergic system mediates the discriminative stimulus effects of cocaine, neither selective D_1 or D_2 dopamine agonists nor selective D_1 or D_2 antagonists substitute reliably for or consistently block these effects. These findings suggest that concurrent activity at these receptor subtypes may underlie this discrimination. Accordingly, it would be expected that simultaneous blockade of these receptors may be necessary to block it fully. The ability of various combinations of the D_1 antagonist, SCH 23390, and the D_2 antagonist, haloperidol, were tested for their ability to block the cocaine stimulus in rats trained to discriminate cocaine (7.5, 10, or 13 mg/kg) from vehicle. Antagonist combinations decreased the percentage of cocaine-appropriate responses 10–95% below the cocaine baseline at doses of the antagonist that were inactive when given separately. These findings support the position that activity at D_1-like and D_2-like receptor subtypes may account for more of the pharmacological action of cocaine than activation of a single dopamine receptor subtype.

Dopamine Drug discrimination learning Cocaine

THE drug discrimination procedure (18,31) is used as a tool to classify drugs according to their discriminative stimulus effects, to provide information regarding the underlying pharmacology and neurochemistry of these effects [(16); for a bibliography see (32)], and to predict subjective effect profiles of compounds in humans (17,20). In this procedure, subjects are trained to discriminate between a drug and vehicle, for instance, make one response following the administration of a drug and another response following the administration of its vehicle. After the discrimination is learned, other drugs may be substituted for the training drug to assess the similarity of their discriminative stimulus effects to those produced by the training drug. Likewise, drugs can be given to block the discriminative stimulus effects of the training drug; results from the substitution and blockade experiments provide clues as to the underlying mechanism of the drug of interest.

The psychomotor stimulant cocaine has been reported to serve as a discriminative stimulus in rats (11), monkeys (25), and pigeons (19). Although it blocks the uptake of dopamine, norepinephrine, and serotonin (10), evidence suggests that the dopamine system primarily mediates cocaine's discriminative stimulus effects (26,28,40). Whereas drugs that block the uptake of norepinephrine (14,25) and serotonin (3,14,25,28) generally do not substitute for cocaine in animals trained to discriminate cocaine from saline, dopamine uptake inhibitors (3,8,13,14,24,25,36,37,41) and the nonselective dopamine agonist apomorphine (11,28,37,42) generally do [although see (3,14,19,36) for partial substitution of norepinephrine uptake inhibitors and (19) for partial substitution of serotonin and dopamine uptake inhibitors].

Until recently, it was believed that there were two classes of dopamine receptors; those that activate adenylyl cyclase, D_1 receptors, and those that inhibit or have no effect on it, D_2 receptors (22). Many agonists and antagonists have since been

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identified to bind to these receptors with relative selectivity. Recently, three more subtypes of dopamine receptors have been identified (33). Although distinct, these new dopaminergic receptor subtypes share molecular characteristics with either D_1 or D_2 receptors and based on these similarities have been grouped into two subfamilies: D_1-like, including D_1 and D_5 subtypes, and D_2-like, including D_2, D_3, and D_4 subtypes. Ligands that bind selectively to these new receptor subtypes are currently being developed.

Given the availability of a variety of compounds that bind to D_1 and D_2 receptor subtypes, much of the work examining the dopaminergic mediation of the discriminative stimulus effects of cocaine has focused on the role that D_1 and D_2 receptor subtypes play in mediating this behavioral effect. Experiments with selective dopamine receptor subtype agonists and antagonists, however, have not confirmed a specific role of either D_1 or D_2 receptors in the discriminative stimulus effects of cocaine (40). A variety of selective D_1 (9,28,35,41) and D_2 (13,35,41) dopamine agonists generally have been reported to substitute only partially for the discriminative stimulus effects of cocaine [see (4,21,24,25) for failure of D_1 agonist substitution]. Interestingly, the D_2 agonist, quinpirole, has been reported to substitute fully (9,37), partially (21,35,41), and not at all (25) for cocaine. In addition, a variety of selective D_1 (3,4,9,23,41) and D_2 (3,4,9,12,28,37) antagonists generally only partially block the stimulus effects of cocaine [see (4,8,11,41) for failure of D_2 antagonists to block].

As noted above, selective D_1 or D_2 dopamine receptor agonists do not reliably substitute for the discriminative stimulus effects of cocaine. In turn, selective dopamine antagonists do not reliably block them. Together, these findings suggest that the separate actions of dopamine at these specific dopamine receptors do not exclusively mediate cocaine's stimulus effects. Instead, the discriminative stimulus effects of cocaine may be mediated by the concurrent activity of dopamine at D_1-like and D_2-like receptor subtypes. Given that a variety of selective ligands acting at D_3, D_4, and D_5 receptors are not yet available, the present experiment explored the combined roles of D_1 and D_2 receptor subtypes in mediating cocaine's discriminative stimulus effects. For example, if the discriminative stimulus effects of cocaine are mediated by the concurrent activity of dopamine at D_1 and D_2 receptors, it might be expected that the simultaneous administration of D_1 and D_2 antagonists would be necessary to fully block cocaine's stimulus effects. Rats were trained to discriminate cocaine (7.5, 10, or 13 mg/kg) from saline within a water-reinforced operant procedure. After the discrimination was stable, the effects of the D_1 antagonist, SCH 23390 (SCH), the D_2 antagonist haloperidol (HAL), and SCH/HAL combinations were tested for their ability to block the discriminative stimulus effects of cocaine. For subjects in group A, antagonism tests were performed against the training dose of cocaine and for subjects in group B they were performed against varying doses of cocaine using a cumulative dosing procedure (5). Consequently, SCH/HAL combinations decreased the percentage of cocaine-appropriate responses 10–95% below the cocaine baseline at doses of each antagonist that were inactive when given separately. This finding was evident in at least one SCH/HAL dose combination tested in each subject in each group.

METHOD

Subjects

The subjects were 12 experimentally naive, female rats of Long-Evans descent, approximately 120 days of age at the beginning of the experiment. The rats were maintained on a 12 L : 12 D cycle (lights on at 0800 h) in rooms at an ambient temperature of 25–26°C. For the duration of the study, subjects were maintained at approximately 90% of prior free-feed body weight by fluid restriction. The subjects were given water supplements following the experimental session to achieve a total of 12–15 ml of water per day. Food was available ad lib in the home cage.

Apparatus

Experimental sessions were conducted in one of three identical 25 × 30 × 18 cm Plexiglas operant chambers. One wall of each chamber contained three equally spaced holes 1.5 cm in diameter, which allowed access to stainless steel drinking tubes (blunted 16 gauge needles). A white light was located 1 cm below each opening. A white houselight was located 9 cm above the center opening. A solenoid valve controlled the delivery of a water reinforcer to the center tube. Experimental contingencies for each chamber were programmed on an Apple IIGS computer, which also recorded all responses made during experimental sessions. This computer was interfaced with the operant chamber through a Med Associates interface (Model 1080-01). Licks on any one of the three tubes in each chamber were registered by three Lafayette drinkometers (Model 58008) whenever a circuit was completed between the chamber floor and any of the tubes. A more detailed description of the apparatus can be found in Mastropaolo et al. (27).

Procedure

Phase 1: shaping. On day 1 of this phase, the houselight and the light below the center drinking tube were illuminated for 10 min, during which time all licks to the center drinking tube resulted in the delivery of a 0.01-ml drop of water. This procedure was repeated daily until licking stabilized on the center tube. At this point, the session consisted of an alternating cycle of 15 s lights-off and 1 min lights-on (houselight and center light). During the lights-off period, licking on the center tube had no programmed consequences. During the lights-on period, each lick on the center tube resulted in the delivery of a 0.01-ml drop of water. This cycle was repeated eight times over the 10-min session. Once licking occurred primarily during the lights-on periods, the lights-off periods were gradually increased from 15 s to 1 min. This cycle was repeated five times over the 10-min session.

Phase 2: forced-choice training. During this phase, subjects were given either an IP injection of cocaine (7.5 mg/kg) or an equivolume injection of distilled water immediately prior to the session. The session began with a 5-min lights-off period, during which time licks had no programmed consequences. This was followed by a 10-min lights-on period, during which the houselight and either the left or right side light were illuminated. A single lick, fixed-ratio (FR) 1, on the illuminated side tube resulted in the termination of the side light and the illumination of the center tube light for approximately 5 s, during which each lick on the center tube resulted in a 0.05-ml drop of water. After 5 s, the same side light was illuminated and the cycle was repeated. Licks on the unlighted tube had no programmed consequences. This sequence was repeated throughout the 10-min lights-on period. For half of the subjects, the illumination of the left tube was paired with cocaine administration and the illumination of the right tube was paired with distilled water administration. The remaining subjects received the opposite condition, for instance, the illumination of the right light was paired with cocaine administra-

tion and the illumination of the left light was paired with distilled water administration. Over sessions, the FR requirement on the side tube was increased gradually by increments of 5 to a final value of FR 20. Either cocaine (C) or distilled water (W) was given each day in the following 8-day sequence: WCCWCWWC. Daily forced-choice training continued until the mean percentage of injection-appropriate responses was greater than 85%.

Phase 3: discrimination training. At the beginning of each session in this phase, subjects were injected with either cocaine or distilled water. The procedure in this phase was similar to that of Phase 2 with the exception that during the 10-min lights-on period, the houselight and both the left and right side lights were illuminated simultaneously. Twenty responses (FR 20) on the injection-appropriate side tube (as determined during Phase 2) resulted in the termination of both side lights and the illumination of the center tube light for approximately 5 s, during which each lick on the center tube resulted in a 0.05-ml drop of water. Licks on the other side tube had no programmed consequences. After water access, the houselight and the left and right side lights again were illuminated. This sequence was repeated throughout the 10-min lights-on period. Daily discrimination training continued until at least 85% of the lick responses made prior to the first water reinforcer were made on the injection-appropriate tube for at least 8 out of 10 discrimination training sessions. If this criterion was not met after several training sessions, the training dose of cocaine was increased to 10 mg/kg and, if necessary, subsequently to 13 mg/kg.

Phase 4: antagonism testing. Subjects were divided randomly into two groups ($n = 6$ per group). On probe sessions during this phase, subjects in group A were injected with either SCH or HAL, alone, or in combination 30-min prior to the administration of the training dose of cocaine or distilled water. Immediately following the cocaine or vehicle injection, subjects were placed into the chamber. Following a 5-min lights-off period, the houselight and both the left and right tube lights were illuminated. After an FR 20 was completed on either the left or right side tube or the lapse of 10 min, all lights were terminated and the session ended. No reinforcers were given on test days. The number of licks made on each tube was recorded. The order of drug testing was SCH (0–0.24 mg/kg), HAL (0–0.1 mg/kg) and SCH/HAL combinations. Doses for the D_1/D_2 combination tests were based on a subject's previous response to the drugs separately. Specifically, a dose of SCH or HAL was chosen to be part of the drug combination if a) following the drug/cocaine combination, responses were similar to that following cocaine alone, for instance, the drug did not antagonize the discriminative stimulus effects of cocaine (or antagonized it by less than 20%); and b) following the drug alone, the rate of responding was not suppressed below one lick per second. For any specific drug or drug combination, the doses were given in a mixed order and tested once unless otherwise indicated. Antagonism test sessions occurred no more than twice a week with at least 2 or 3 training days between each test.

Subjects in group B also received SCH, HAL, or a SCH/HAL combination either alone or prior to cocaine during antagonism test sessions; however, unlike subjects in group A, subjects in this group were tested using cumulative doses of cocaine (5). Utilizing a cumulative dosing procedure allowed for a four-point cumulative dose-response function for cocaine to be determined in a single session. To ensure that subjects could change drug-appropriate levers within a test session, subjects initially received cumulative dosing probe sessions consisting of a series of distilled water and/or cocaine injections. On days in which distilled water was tested, subjects received four alternating 5-min lights-off/2-min lights-on components within a 28-min session. Immediately prior to each lights-off period, subjects were given an IP injection of distilled water (1 ml/kg). Vehicle-appropriate responses were reinforced during each lights-on component. This procedure was repeated on subsequent probe sessions until 85% of responses made prior to the first reinforcer during each lights-on component were vehicle-appropriate. Once this criterion was met, a cocaine probe was given. Specifically, distilled water injections were given immediately prior to each of the first three lights-off components and an injection of the training dose of cocaine was given prior to the fourth lights-off component. Vehicle-appropriate responses were reinforced during the first three lights-on components, and cocaine-appropriate responses were reinforced during the fourth lights-on component. If subjects displayed 15% or less cocaine-appropriate responses prior to the first reinforcer during the first three components and 85% or greater prior to the first reinforcer of the fourth component, antagonism tests began (see below). If this criterion was not met, discrimination training continued and these probes were repeated on subsequent sessions.

Immediately prior to each lights-off period at the outset of antagonism testing, subjects were injected with incremental doses of cocaine that cumulated to 1.8, 3.2, 5.6, and 10 mg/kg (i.e., doses of 1.8, 1.4, 2.4, and 4.4 mg/kg) over the same four successive lights-off/lights-on components as described above. After the dose-response function was obtained, antagonism probes began. On these days, subjects were injected with SCH (0.01–0.24 mg/kg), HAL (0.024–0.1 mg/kg), or a SCH/HAL combination 30 min prior to receiving the same incremental doses of cocaine or its vehicle. Doses for the D_1/D_2 combination tests were based on a subject's previous response to the drugs separately. Specifically, a SCH/HAL dose combination was chosen if a) following at least one SCH/cocaine or HAL/cocaine combination discriminative control during each of the four components was similar to that of a cocaine training session, for instance, at least one drug did not antagonize the discriminative stimulus effects of cocaine (or antagonized it by less than 20%); and b) following the drug alone, the rate of responding during each of the four components of the session was not suppressed below one lick per second. To ensure operant responding throughout each of the four components of the session, the completion of an FR 20 on either side tube resulted in reinforcement during each component of the dose-response and antagonism probe sessions. Cumulative dosing antagonism test sessions occurred no more than twice a week with at least 2 or 3 training days between each test.

Data are presented as the percentage of responses made on the cocaine-appropriate tube. Results from test sessions are compared to responses made following the training dose of cocaine (cocaine baseline data). Given the degree of individual variability among subjects, data are presented as individual subject findings.

Drugs

Cocaine hydrochloride was generously supplied to our laboratory by The National Institute on Drug Abuse (NIDA), Rockville, MD. Haloperidol was purchased from McNeil Pharmaceuticals, Fort Washington, PA, and SCH 23390 hydrochloride was purchased from Research Biomedicals International (RBI), Natick, MA. Cocaine and SCH 23390 were

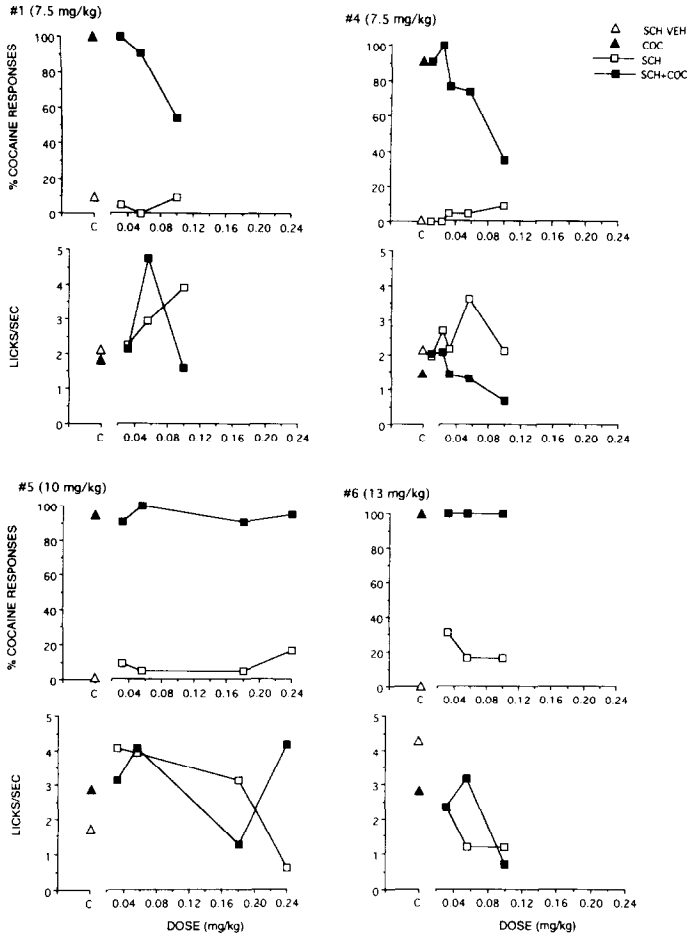

FIG. 1. The percentage of cocaine-appropriate responses and rates of licking made prior to the first reinforcer for four subjects in group A following various doses of SCH (0–0.24 mg/kg) alone (open squares) and in combination with the training dose of cocaine (closed squares). The triangles represent responses and lick rates following the SCH vehicle (open triangles) and the training dose of cocaine (closed triangles). These representative baseline points occurred on the 2 days immediately prior to testing with this compound. The training dose of cocaine for each subject is indicated in parentheses in the top left-hand corner of each set of graphs. Data are shown for four of the six subjects in group A. Subject 2 did not acquire the cocaine discrimination and subject 3 died prior to antagonism testing.

prepared in distilled water. Haloperidol was prepared in lactic acid (1.0%). All drugs were administered intraperitoneally (IP) in a volume of 1 ml/kg.

RESULTS

The shaping and forced-choice training phases were completed for all subjects within 20 and 35 sessions, respectively. The rate of acquisition of the discrimination (52 to 176 sessions) and the terminal dose of cocaine (7.5, 10, or 13 mg/kg) varied for individual subjects. For a single subject (subject 6), when the training dose of cocaine was increased to 13 mg/kg cocaine-appropriate responses averaged approximately 40% after vehicle administration. Hence, for this subject discrimination training continued until cocaine-appropriate responses were at least 85% following cocaine and, at most, 40% following the vehicle for at least 8 out of 10 consecutive days.

Antagonism: Group A

Originally, six subjects (subjects 1–6) comprised group A. However, only data from four subjects (subjects 1, 4, 5, and 6) are included in the analysis of antagonism testing with SCH and HAL separately. Subject 2 did not acquire the cocaine discrimination; its licking responses were biased to one side tube despite the injection given. Subject 3 died prior to antagonism testing; the cause of death was unknown. Data from three subjects (subjects 1, 5, and 6) are included in the analysis of antagonism with SCH/HAL combinations. Subject 4 did not receive, SCH/HAL combinations with cocaine because when SCH/HAL combinations (as low as 0.01 mg/kg of SCH and 0.024 mg/kg of HAL) were tested alone no lick responses were made.

SCH 23390. SCH (0–0.24 mg/kg) given in combination with the training dose of cocaine (Fig. 1) partially antagonized

the discriminative stimulus effects of cocaine in two subjects; for instance, cocaine-appropriate responses decreased from 85-100% (baseline) to 40-80%. For subject 1, cocaine-appropriate responses decreased to 58% at 0.1 mg/kg of SCH. For subject 4, responding decreased to 80, 78, and 40% at 0.032, 0.056, and 0.1 mg/kg of SCH, respectively. Antagonism of cocaine's discriminative stimulus effects by any dose of SCH was not displayed in subjects 5 and 6. For all subjects, doses of SCH alone produced vehicle-appropriate responses. Following SCH alone and SCH + cocaine, lick rates for all subjects did not change consistently as the dose of SCH increased.

Haloperidol. HAL (0-0.1 mg/kg) given in combination with cocaine (Fig. 2), completely antagonized cocaine's discriminative stimulus effects in two subjects; for instance, cocaine-appropriate responses decreased from the cocaine baseline to below 15%. For subject 1, cocaine-appropriate responses decreased to 4.8% at 0.056 mg/kg and for subject 4 responses decreased to 0% at 0.1 mg/kg. Haloperidol (at any dose) failed to antagonize the discriminative stimulus effects of cocaine in subjects 5 and 6. For all subjects, doses of HAL alone produced vehicle-appropriate responses. Following HAL alone and HAL + cocaine, lick rates for all subjects did not change consistently as the dose of HAL increased.

Interestingly, antagonism (or the lack of antagonism) of cocaine's discriminative stimulus effects by SCH and HAL was displayed in the same subjects. Antagonism was only displayed by subjects 1 and 4 who were trained with the lower dose of cocaine (7.5 mg/kg).

SCH 23390/haloperidol combinations. Figure 3 presents one SCH/HAL combination for subject 1. As illustrated, neither 0.032 mg/kg of SCH nor 0.032 mg/kg of HAL antagonized cocaine's discriminative stimulus effects when given alone prior to the training dose of cocaine. However, the SCH/HAL combination partially antagonized these effects, decreasing cocaine-appropriate responses from the cocaine baseline (100%) to 54%. Subject 1 died after only one SCH/HAL combination test; the cause of death was unknown.

Figure 4 presents four SCH/HAL combinations for subject 5. As illustrated in the top left panel, neither 0.032 mg/kg of SCH nor 0.032 mg/kg of HAL alone antagonized cocaine's discriminative stimulus effects. However, the SCH/HAL combination partially antagonized these effects, decreasing cocaine-appropriate responses from the cocaine baseline to

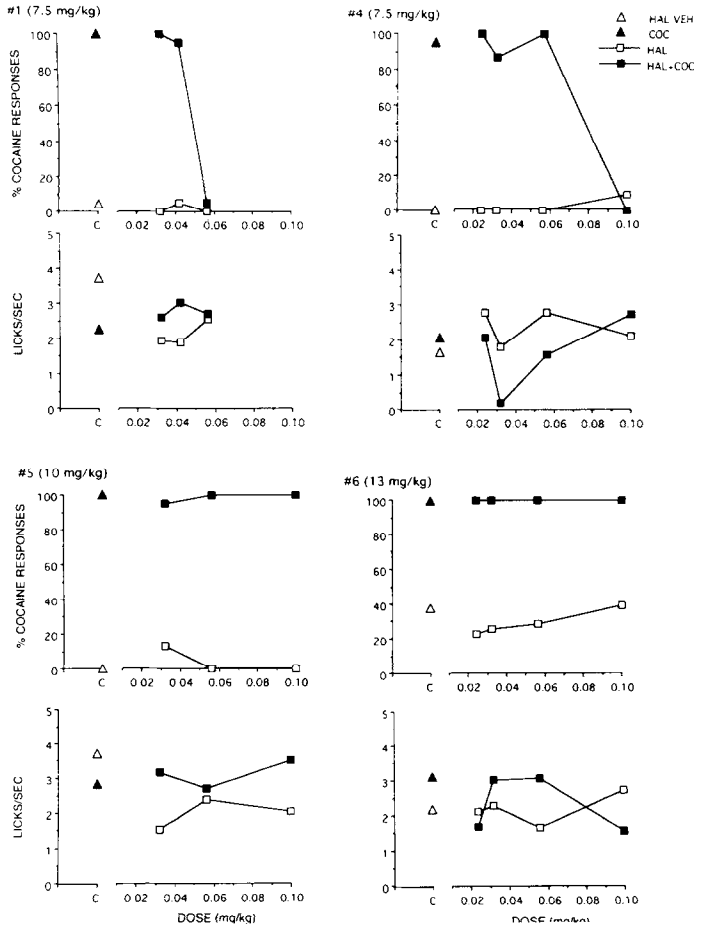

FIG. 2. The percentage of cocaine-appropriate responses and rates of licking made prior to the first reinforcer for four subjects in group A following various doses of HAL (0-0.1 mg/kg) alone (open squares) and in combination with the training dose of cocaine (closed squares). Other details as in Fig. 1.

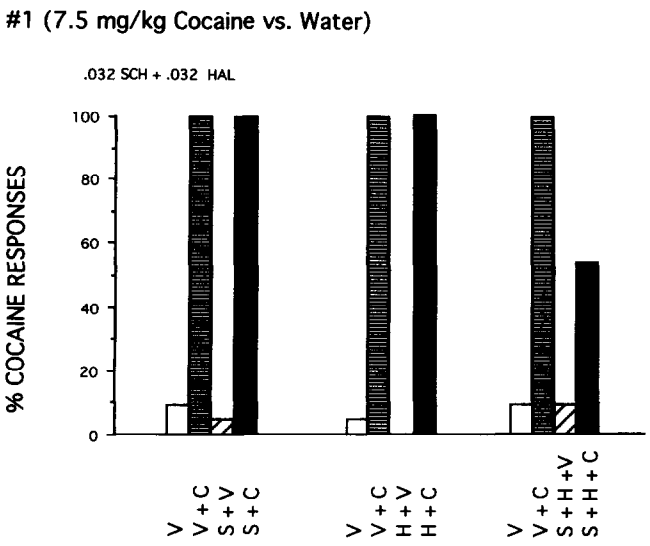

FIG. 3. Effects of SCH, HAL, or SCH/HAL combinations on the percentage of cocaine-appropriate responses made prior to the first reinforcer for subject 1: SCH (S; the first set of four bars), HAL (H; the second set of four bars) and the SCH/HAL combination (S/H; the third set of four bars). V: effects of saline + antagonist vehicle; V + C: effects of antagonist vehicle + cocaine (these representative baseline points occurred on the 2 days immediately prior to testing with this compound or combination.); S + V, H + V or S + H + V: effects of antagonist + vehicle; S + C, H + C or S + H + C: effects of antagonist + cocaine. The specific doses of SCH and HAL are noted in the top left-hand corner of the panel, respectively.

70%. A higher dose of HAL (0.056 mg/kg; top, right panel) also did not antagonize cocaine's effects. However, when 0.032 mg/kg of SCH was given in combination with this dose of HAL on three separate occasions, varying results were obtained. On the first test, cocaine was completely antagonized (i.e., cocaine-appropriate responses were reduced from the cocaine baseline to 0%). To verify this finding, this combination was repeated. However, on the two subsequent antagonism tests cocaine's stimulus effects were not antagonized (i.e., cocaine-appropriate responses were at 100%) or were slightly antagonized (i.e., cocaine-appropriate responses were at 83.3%). The bottom two panels illustrate higher SCH/HAL dose combinations. Neither dose of SCH or HAL alone antagonized cocaine's stimulus effects. Further, neither of the two dose combinations affected cocaine-appropriate responses.

Figure 5 presents three SCH/HAL combinations for subject 6. As illustrated in the top panel, neither 0.032 mg/kg of SCH nor 0.024 mg/kg of HAL alone antagonized cocaine's discriminative stimulus effects. However, this combination completely antagonized cocaine's stimulus effects, for instance, cocaine-appropriate responses decreased from the cocaine baseline to 37.5% (for subject 6, control levels of vehicle-appropriate responses were 40%). Larger doses of HAL (0.032 and 0.056 mg/kg) alone did not antagonize cocaine (middle and bottom panels, respectively). The combination of SCH (0.032 mg/kg) and these higher doses of HAL produced partial (0.032 mg/kg of HAL; middle panel) or no (0.056 mg/kg of HAL; bottom panel) antagonism.

Antagonism: Group B

Six subjects (subjects 7–12) originally comprised group B. However, only data from two subjects (subjects 7 and 11) in this group were included in the final analysis. Subject 8 did not acquire the cocaine discrimination at 13 mg/kg of cocaine and was removed from the study. Although subjects 9 and 10 acquired the discrimination, performance did not remain stable following preliminary cumulative dosing testing; therefore, no antagonism testing was conducted. Subject 12 died prior to antagonism testing; the cause of death was unknown.

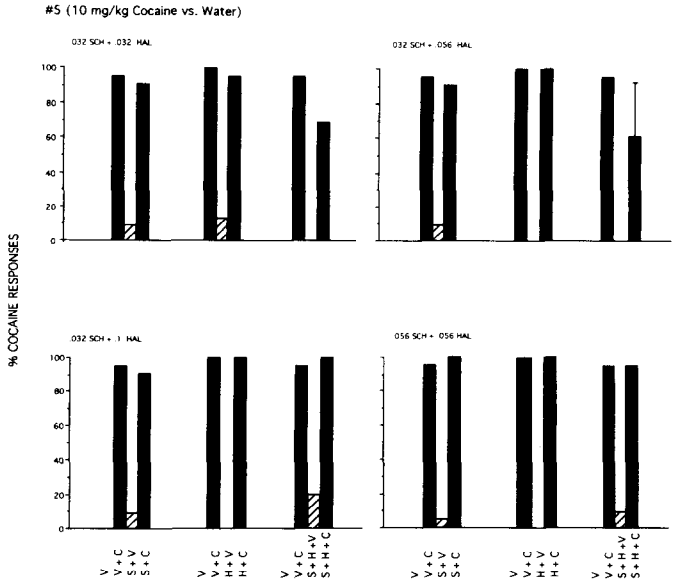

FIG. 4. Effects of three SCH/HAL dose combinations for subject 5. The error bar in the top, right panel represents the mean (±SEM) of three determinations of S + H + C. Other details as in Fig. 3.

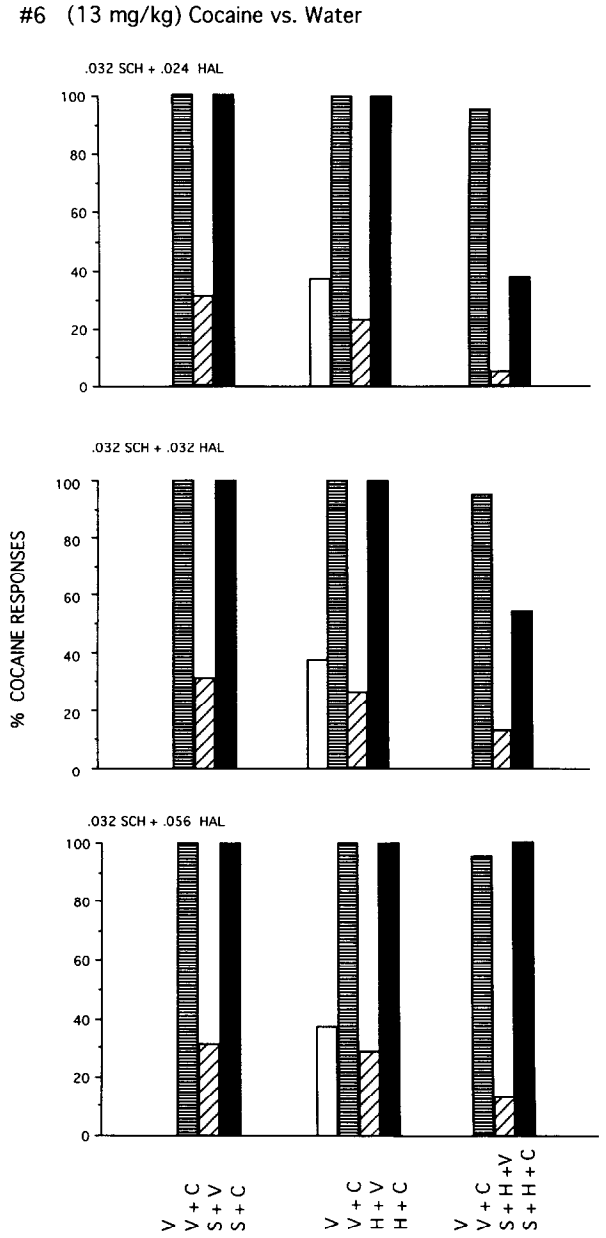

FIG. 5. Effects of three SCH/HAL dose combinations for subject 6. Other details as in Fig. 3.

Because only data from a small number of subjects could be used, Subject 5 from group A was also used in the cumulative dosing procedure. Hence, a total of three subjects comprised this phase of the study.

Figure 6 presents three SCH/HAL combinations for subject 5 under the cumulative dosing regimen. Successive panels of this figure show the effects of increasing doses of SCH in combination with 0.032 mg/kg of HAL. Cocaine alone produced dose-dependent increases in the percentage of cocaine-appropriate responses with 5.6 and 10 mg/kg of cocaine producing responses above 85%. At 5.6 mg/kg of cocaine, neither 0.0032 mg/kg of SCH nor 0.032 mg/kg of HAL antagonized cocaine's effects (top panel). However, this SCH/HAL combination completely antagonized the stimulus effects of this dose of cocaine, decreasing cocaine-appropriate responses from 100 to 4.76%. At 10 mg/kg of cocaine, responses were unaffected by this SCH/HAL combination, for instance, responses were similar to that following SCH or HAL alone in combination with cocaine. As illustrated in the middle panel, when a higher dose of SCH (0.024 mg/kg) was combined with 0.032 mg/kg of HAL, responses were reduced from 100% following 5.6 mg/kg of cocaine to 0%, an effect similar to that following the combination of SCH and cocaine. At 10 mg/kg of cocaine, responses were unaffected following this SCH/HAL combination. As illustrated in the bottom panel, when SCH at 0.032 mg/kg was combined with 0.032 mg/kg of HAL responses were reduced from 100% following 5.6 mg/kg of cocaine to 0% and were similar to that following SCH plus cocaine. At 10 mg/kg of cocaine, neither 0.032 mg/kg of SCH nor 0.032 mg/kg of HAL alone antagonized cocaine's effects. However, this SCH/HAL combination partially antagonized cocaine's effects, decreasing responses from 100% following 10 mg/kg of cocaine to 33%.

Figure 7 presents two SCH/HAL combinations for subject 7 under the cumulative dosing regimen. Cocaine alone produced dose-dependent increases in the percentage of cocaine-appropriate responses with 5.6 and 10 mg/kg of cocaine producing responses at 41.18 and 100%, respectively. At 5.6 mg/kg of cocaine, responses following the SCH/HAL combination of 0.0032 and 0.032 mg/kg (top panel) were above 90%, similar to that following SCH alone and above that following 5.6 mg/kg of cocaine alone. At 10 mg/kg of cocaine, neither 0.0032 mg/kg of SCH nor 0.032 mg/kg of HAL antagonized cocaine's effects. However, this combination completely antagonized it, decreasing cocaine-appropriate responses from 100 to 4.8%. Interestingly, this dose of SCH alone (and in combination with HAL) appeared to potentiate the effects of cocaine at 5.6 mg/kg, while this combination antagonized the effects at 10 mg/kg of cocaine. As illustrated in the bottom panel, a higher dose of SCH (0.032 mg/kg) combined with 0.032 mg/kg of HAL minimally affected responses at 5.6 mg/kg of cocaine and was similar to that following the combination of HAL and cocaine. At 10 mg/kg of cocaine, responses decreased from 100% to 9.1% following this combination. This antagonism was slightly greater than that following SCH (23.1%) and markedly greater than HAL (100%) in combination of cocaine.

Figure 8 presents two SCH/HAL combinations for subject 11 under the cumulative dosing regimen. Cocaine alone produced dose-dependent increases in the percentage of cocaine-appropriate responses with 3.2, 10, and 13 mg/kg of cocaine producing responses above 85%. At 3.2 mg/kg of cocaine, the SCH/HAL combination of 0.0032 and 0.0056 mg/kg (top panel) decreased responses from 87 to 0%, an effect similar to that following the combination of HAL and cocaine. At 10 mg/kg of cocaine, responses decreased from 100% following cocaine to 66.7% following this combination. This antagonism was slightly greater than that following SCH (100%) and HAL (76.9%) in combination with cocaine. At 13 mg/kg of cocaine, responses were unaffected following this combination and were similar to that when cocaine was given with either SCH or HAL. As illustrated in the bottom panel, a higher dose of HAL (0.024 mg/kg) combined with 0.0032 mg/kg of SCH decreased responses from 87% following 3.2 mg/kg of cocaine to 0% and were similar to that following HAL alone. At 10 mg/kg of cocaine, responses were unaffected following this combination and were similar to that following SCH or HAL alone. At 13 mg/kg of cocaine, nei-

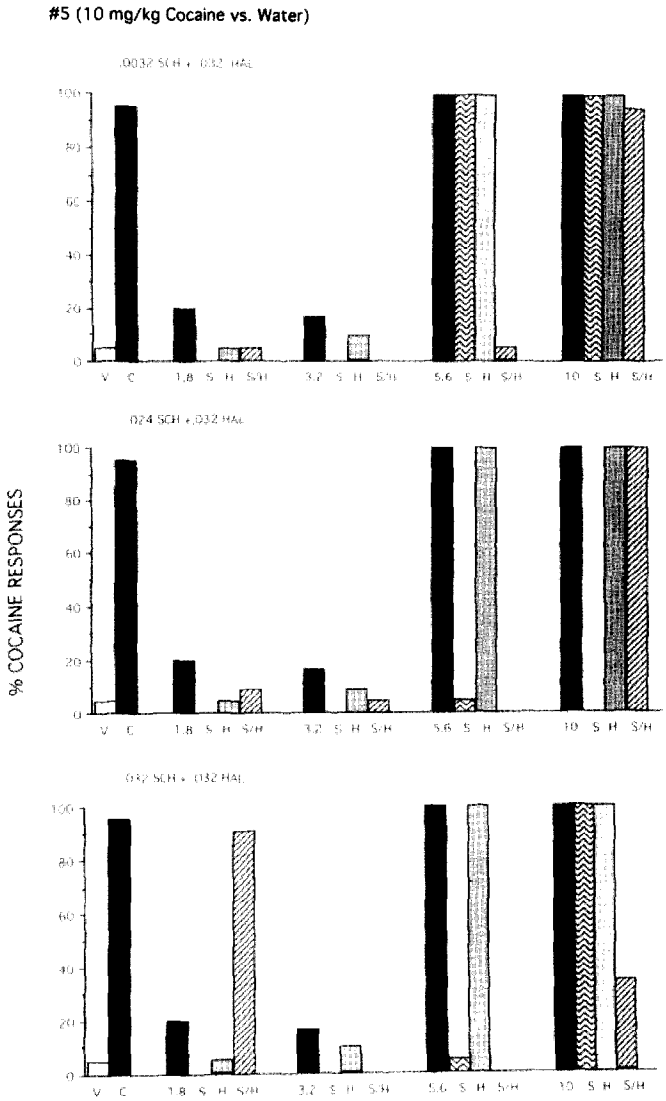

FIG. 6. Effects of SCH, HAL, or a SCH/HAL combination on the discriminative stimulus effects of a range of doses of cocaine for subject 5. Each panel presents the percentage of cocaine-appropriate responses made prior to the first reinforcer. Effects of the cocaine vehicle and the training dose of cocaine are shown as reference as the first and second bars, respectively. The next four sets of bars represent responses following a cumulative dose of cocaine (1.8, 3.2, 5.6, or 10 mg/kg) alone or with SCH (S), HAL (H) or the SCH/HAL (S/H) combination. The specific doses of SCH and HAL are noted in the top left-hand corner of the panel, respectively.

ther SCH nor HAL antagonized cocaine's effects. However, this combination decreased responses from 100% following cocaine at 13 mg/kg to 80%.

DISCUSSION

That selective dopamine uptake inhibitors and the nonselective dopamine agonist apomorphine substitute fully for the discriminative stimulus effects of cocaine (see Introduction) suggest that dopaminergic actions are important to the discriminative control of behavior by cocaine. As demonstrated previously (3,4,9,41) and in the present experiment (Figs. 1 and 2), however, neither the D_1 antagonist, SCH 23390, nor the D_2 antagonist, haloperidol, when tested alone consistently blocked the discriminative stimulus effects of cocaine. Despite the reports that D_1 and D_2 antagonists do not consistently block the discriminative stimulus effects of cocaine (3,4,9, 12,23,28,37), the results of the present study demonstrated greater antagonism of these effects following a D_1/D_2 antagonist combination than following either antagonist alone.

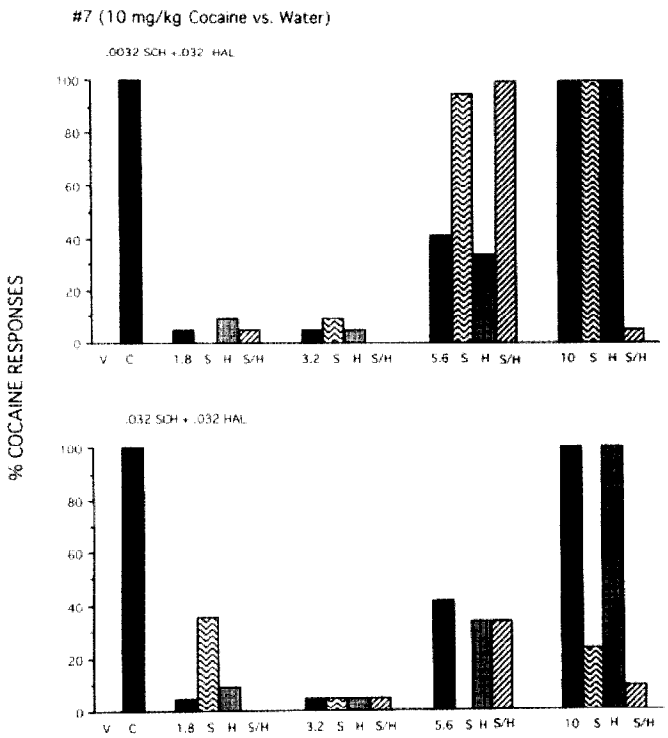

FIG. 7. Effects of two SCH/HAL combination tests for subject 7 following cumulative doses of cocaine (1.8, 3.2, 5.6, or 10 mg/kg). Other details as in Fig. 5.

These findings suggest that concurrent actions of dopamine at D_1-like and D_2-like receptor subtypes contribute to the discriminative stimulus effects of cocaine.

Although some SCH/HAL antagonist combinations produced greater antagonism of the discriminative stimulus effects of cocaine than either antagonist alone, the degree of antagonism (partial or full) and the dose of cocaine at which antagonism could be demonstrated (training or lower dose) varied among subjects (see Table 1 for a summary of these findings). For example, full antagonism of cocaine's effects at the training dose was demonstrated in two subjects (group A, subject 6; group B, subject 7). Full antagonism at a dose less than that of the training dose was demonstrated in one subject (group B, subject 5). Partial antagonism was displayed at the training dose in two subjects (group A, subject 1; group B, 11). However, given that in these cases full antagonism was only displayed at comparatively low SCH/HAL dose combinations testing lower SCH/HAL dose combinations in these subjects may have yielded full antagonism.

As mentioned above, antagonism of the discriminative stimulus effects of cocaine was displayed at comparatively low SCH/HAL dose combinations. At higher dose combinations, these combinations either failed to antagonize cocaine's effects or did not produce greater antagonism than either one or both of the selective antagonists alone. Although the reason for this finding is unknown, it does suggest that at higher dose combinations additional factors may be operating. For example, higher dose combinations failed to antagonize cocaine's stimulus effects in some instances where the combination was being tested against the training dose of cocaine. This occurred in subjects in which combinations were only tested against the training dose of cocaine (group A; subjects 5 and 6) and those in which combinations were tested against cumulative doses of cocaine (group B; subjects 5 and 11). It is possible that at this dose combination, blockade of dopamine uptake was sufficient to overcome receptor blockade. Because higher doses of dopamine antagonists are behaviorally disruptive (38,39), it may not have been possible to assess the effects of greater levels of receptor blockade. In other cases, one of the antagonists alone completely blocked cocaine's discriminative stimulus effects and the D_1/D_2 combination could not antagonize these effects to any further extent than was displayed by the selective antagonist alone. This was displayed in subjects in group B (subjects 5 and 11) at doses of cocaine below the training dose. In yet other instances, the antagonism displayed by the D_1/D_2 combination was less than that displayed by one of the antagonists and more than (or equal to) that displayed by the other antagonist (group B; subject 7). In such cases, it is possible that the D_1 and D_2 antagonists were interacting in an oppositional manner such that concurrent blockade of both receptor subtypes may result in an antagonism intermediate to that displayed by each antagonist alone. This phenomenon has been demonstrated in other preparations [e.g., (15,29,30)].

Although these findings support the position that the concurrent actions of dopamine at D_1-like and D_2-like receptor subtypes contribute to the discriminative stimulus effects of cocaine, it does not rule out the possibility that other receptor systems (norepinephrine and serotonin) may also contribute to these effects. It has been suggested by others that although the dopaminergic system may be the primary mediator of the discriminative stimulus effects of cocaine, noradrenergic and serotonergic receptor systems may play a modulatory role (14,34,36). For example, Cunningham and Callahan (14) recently reported that whereas the dopamine uptake inhibitor, GBR 12909, substituted for the cocaine stimulus in rats [see also (3,8,25,41)], neither the norepinephrine uptake inhibitor, desipramine, nor the serotonin uptake inhibitor, fluoxetine, did [see also (3,25)]. However, when small doses of each uptake inhibitor were combined with cocaine, all three potentiated cocaine's stimulus effects [though see (34)], suggesting that these neurotransmitter systems may play some modulatory role in mediating cocaine's discriminative stimulus effects. Furthermore, Terry, Witkin, and Katz (36) recently demonstrated that norepinephrine uptake inhibitors and D_1 agonists fully substituted for the discriminative stimulus effects of cocaine at a low training dose of cocaine (3 mg/kg) in rats, whereas others have found little to no substitution of these compounds at a training dose of 10 mg/kg (3,9,14, 28,41). That full substitution was demonstrated at a low dose of cocaine with these compounds is in accordance with some of the findings in the present study. For example, antagonism of cocaine's effects following SCH and HAL given separately was only displayed in those subjects that were trained with the lower dose of cocaine (7.5 mg/kg). These findings all seem to suggest that the cocaine stimulus may be the result of some combination of activity at dopamine (D_1-like and D_2-like receptor subtypes), norepinephrine, and serotonin receptors. Although it remains unknown under what circumstances each might operate, it seems that this effect is highly sensitive to both the training dose of cocaine and the dose of the test compounds.

Dynamic interplay between dopamine receptor subtypes has been suggested previously in work examining the role of

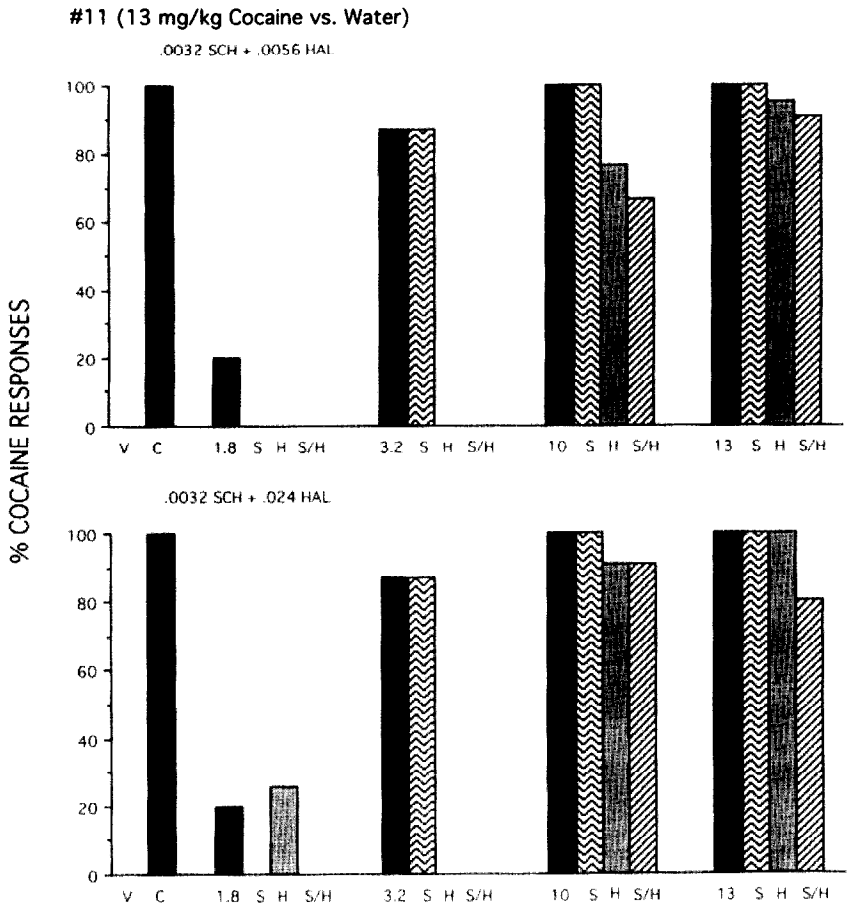

FIG. 8. Effects of two SCH/HAL combination tests for subject 11 following cumulative doses of cocaine (1.8, 3.2, 10, or 13 mg/kg). Other details as in Fig. 5.

D_1 and D_2 agonists on dopamine-mediated behaviors where synergistic interactions between selective dopamine agonists have been reported (7). For example, Braun, Barone, and Chase (6) demonstrated that although the D_1 agonist, SKF 38393, did not induce rotation in rats with unilateral quinolinic acid lesions in the striatum, SKF 38393 enhanced the turning elicited by the D_2 agonist quinpirole. D_1 agonists have also been reported to potentiate stereotyped behaviors elicited by D_2 agonists. For example, Arnt, Hyttel, and Peeregaard (2) demonstrated that although the D_1 agonists, SKF 38393, SKF 75670, and Lu 24-040, alone did not induce stereotyped behaviors, the D_2 agonist, quinpirole, induced stereotypy in rats. When each D_1 agonist was combined with quinpirole, oral stereotypies (e.g., licking and occasional biting) were also observed in these animals. These drug interactions are consistent with the observation that the mixed D_1/D_2 agonist, apomorphine readily induces oral stereotypies (1). That the stereotypies produced by an SKF 38393/quinpirole combination were blocked completely by either the D_1 antagonist, SCH 23390, or the D_2 antagonist, YM 09151-2, suggests that the production of these behaviors was a result of the synergistic interaction between the D_1 and D_2 receptors (2).

Although it has been demonstrated that some dopamine-mediated behaviors (e.g., rotation and stereotypies) are produced by the synergistic interaction of dopamine at D_1 and D_2 receptor subtypes, it is not clear whether such an interaction occurs in the mediation of the discriminative stimulus effects of cocaine. Specifically, Spealman et al. (35) examined the ability of varying combinations of the D_1 agonist, SKF 81297, and the D_2 agonist, (+)-PHNO, to substitute for the discriminative stimulus effects of cocaine in monkeys trained to discriminate cocaine from saline within a food-reinforced operant procedure. It was reported that the maximal levels of cocaine-appropriate responses following the D_1 and D_2 agonists approximated 73 and 60%, respectively, when given separately. When these D_1 and D_2 agonists were combined, lower doses of the compounds were generally required to achieve the same maximal level of cocaine-appropriate responses, suggesting that D_1 and D_2 receptor subtypes were interacting to produce the discriminative stimulus effects of cocaine. Accordingly, it would be expected that blockade of either receptor would block to some extent the cocaine cue. However, as demonstrated in the present study and by others (3,4,9,41), blockade of the discriminative stimulus effects of cocaine by either D_1 or D_2 antagonists does not always occur.

Thus, it appears from these data and others that the relationship between the D_1 and D_2 dopamine subtypes in producing dopaminergically mediated behaviors is complex and is

TABLE 1

SUMMARY OF ANTAGONISM TESTS

Group A Subject	SCH	HAL	SCH/HAL
1	Partial 0.1	Full 0.056	Partial 0.032 + 0.032
4	Partial 0.032–0.1	Full 0.1	NT*
5	None	None	Partial 0.032 + 0.032 0.032 + 0.056 None 0.032 + 0.1 0.056 + 0.056
6	None	None	Full 0.032 + 0.024 Partial 0.032 + 0.032 None 0.032 + 0.056

Group B Subject	Cocaine (mg/kg) 1.8	3.2	5.6	10	13
5	NA†	NA	Full 0.0032 + 0.032	Partial 0.032 + 0.032	NT
7	NA	NA	NA	Partial 0.032 + 0.032 Full 0.0032 + 0.032	NT
11	NA	NA	NT	Partial 0.0032 + 0.0056	Partial 0.0032 + 0.024

Summary of antagonism tests for each subject tested in Groups A and B. The tabled entry presented for subjects in Group A is the greatest degree of antagonism (full, partial, or none) produced by various doses of SCH, HAL, or the SCH/HAL combination against the training dose of cocaine. The tabled entry presented for subjects in Group B is the greatest degree of antagonism produced by SCH/HAL combinations against cumulative doses of cocaine. Data for the SCH/HAL combinations are presented as SCH + HAL, respectively.

*NT = not tested.

†NA = not applicable.

not always consistent across behaviors. In some instances (i.e., rotation and stereotypies) the relationship appears clearly synergistic (see above) and in others (i.e., mediation of the discriminative stimulus effects of cocaine) it does not (see above). Additionally, the effects of selective dopamine agonists often contrast with the ability of selective dopamine antagonists to alter the behavioral effects of cocaine [cf. (42); see the introductory paragraphs]. For example, Witkin et al. (42) showed consistent partial substitution by both D_1 and D_2 agonists, but D_2 blockade was not effective in partially attenuating the discriminative stimulus effects of cocaine. Although ongoing dopaminergic tone may be critical in mediating certain behaviors, dopaminergic actions at other dopamine receptor subtypes and/or nondopaminergic synapses may be involved (14,34,36). The nature of these discrepancies remains to be fully elucidated.

In conclusion, the present data support the position that the concurrent activity of dopamine at D_1 and D_2 receptor subtypes can be important to the mediation of the discriminative stimulus effects of cocaine by the demonstration of greater antagonism of the discriminative stimulus effects of cocaine following a D_1/D_2 antagonist combination than following either antagonist alone. However, the conditions under which the D_1 and D_2 antagonists produce greater effects than either drug alone appear to be dependent upon the dose of cocaine and the individual animal studied. Detection of such interactions may be also limited by the pronounced behavioral disrupting effects of dopamine antagonists (38,39). The drug interaction experiments reported here, thus, support the conclusion of previous investigators indicating that the indirect actions of cocaine at D_1 and D_2 receptors alone cannot account for the discriminative stimulus effects of cocaine.

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Animals used in this study were maintained in facilities at The American University. All experimentation was conducted in accordance with the guidelines of the Institutional Care and Use Committee of the Division of Intramural Research, National Institute of Drug Abuse, NIH, and the guide for Care and Use of Laboratory Animals of the Institute of Laboratory Animals Resources, National Research Council, Department of Health, Education and Welfare, Publication (NIH) 85-23, revised 1985.

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