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BRIEF COMMUNICATION

# Stimulus Effects of *d*-Amphetamine 1: DA Mechanisms

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VAN GROLL, B. J. AND J. B. APPEL. *Stimulus effects of* d-*amphetamine 1: DA mechanisms.* PHARMACOL BIOCHEM BEHAV **43**(3) 967-973, 1992. – As part of a continuing effort to assess the role of monoaminergic neuronal systems in the subjective effects of CNS stimulants, 10 rats trained to discriminate 1.0 mg/kg *d*-amphetamine from saline were treated with compounds that act through different dopaminergic mechanisms. In substitution (generalization) tests, 20 mg/kg of the dopamine (DA) uptake inhibitor GBR 12909 mimicked the training drug completely; at a dose of 15 mg/kg, GBR 12909 substituted for *d*-amphetamine incompletely. Neither the $D_1$ agonist SK&F 38393 (1, 10 mg/kg) nor the $D_2$ agonist quinpirole (LY 171555; 0.05-0.2 mg/kg) had amphetamine-like effects. When given in combination with the training drug, the $D_1$ antagonist SCH 23390 blocked the amphetamine cue completely at a dose of 0.05 mg/kg but did not have significant effects at higher or lower doses; the $D_2$ antagonist metoclopramide did not block *d*-amphetamine at any dose tested (1-5 mg/kg). These data indicate that: a) The discriminable effects of *d*-amphetamine are due, at least in part, to inhibition of DA uptake; b) direct stimulation of either $D_1$ or $D_2$ receptor sites is not sufficient to evoke *d*-amphetamine-like responding; and c) blockade of $D_1$ receptors attenuates the subjective effects of *d*-amphetamine to a greater extent than blockade of $D_2$ receptors.

*d*-Amphetamine CNS stimulants Dopamine DA uptake DA receptors Drug discrimination
SK&F 38393 Quinpirole SCH 23390 Metoclopramide Rats

CNS stimulants such as cocaine and *d*-amphetamine have many common actions, not the least of which is to increase synaptic concentration of dopamine (DA) by inhibiting its uptake into neurons (39) originating in the ventral tegmentum and projecting to the nucleus accumbens, ventral pallidum, and frontal cortex (33,40,46,50). Indeed, the reinforcing effects and abuse potential of cocaine have been attributed to this mechanism (57), primarily because the ability of this and related drugs to maintain self administration parallels their affinity for the DA transporter (42,43). Recent evidence suggests that the discriminative stimulus effects of cocaine are also related to inhibition of DA uptake (8,14,31). The most reliable generalization of the cocaine cue in both rats (8,14) and rhesus monkeys (59) occurs to compounds that act primarily by inhibiting DA uptake (mazindol, bupropion, nomifensine, GBR 12909); moreover, the order of potency of this generalization is again correlated with affinity for the DA transport site (14).

The mechanisms underlying the behavioral effects of *d*-amphetamine and other phenylethylamines are less clear than those of cocaine. While these stimulants inhibit DA, norepinephrine (NE), and serotonin [5-hydroxytryptamine (5-HT)] uptake, their inhibitory effects are not correlated with their reinforcing properties (42). The ability of *d*-amphetamine to release newly synthesized DA and increase its accumulation in storage pools (26) may have some relevance in vivo: Injection of *d*-amphetamine directly into either the nucleus accumbens or corpus striatum causes both an increase in DA release (32) and a 150% increase in self-stimulation of these areas (15); moreover, chronic administration has greater effects than acute administration (32). Relatively low doses of *d*-amphetamine also increase DA synthesis and metabolism, as measured by 3,4-dihydroxyphenylacetic acid (DOPAC) efflux in conscious, freely moving rats; while this effect occurs primarily in the striatum, less pronounced increases also occur in the nucleus accumbens and olfactory tubercule (41). Thus, it is possible, if not likely, that the behavioral effects of *d*-amphetamine are related to mechanisms other than or in addition to inhibition of neurotransmitter uptake.

The present research is concerned with the role of different DA mechanisms in the discriminative stimulus effects of *d*-amphetamine, which appear to be similar (23,25,35,49,50,58)

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but not identical (21) to those of cocaine. Both compounds also appear to interact in a similar but not identical manner with DA receptors (13): DA agonists (apomorphine, bromocriptine, lisuride, and piribedil) produce no more than 70% drug-appropriate responding in animals trained to discriminate either of these drugs from saline (19,28,36); $D_2$ agonists such as quinpirole (LY 171555) and pergolide mimic both *d*-amphetamine and cocaine to a greater extent than $D_1$ agonists (5–8,9,16,31,41,45,52) and both compounds are blocked by the $D_1$ antagonist SCH 23390 (2,16,30). The putatively selective $D_2$ antagonist haloperidol appears to attenuate the effects of *d*-amphetamine more reliably (7,18,19,38) than those of cocaine (8,13) and it has been shown that the ability of this neuroleptic to block the reinforcing effects of medial forebrain stimulation is positively correlated with its affinity for the $D_2$ receptor (28). However, because haloperidol has considerable affinity for 5-$HT_1$, 5-$HT_2$, NE $\alpha$-, and $D_1$ receptors (39), the role of $D_2$ receptors in the subjective effects of CNS stimulants is anything but clear.

To further assess the role of different DA mechanisms in the stimulus properties of *d*-amphetamine, the DA uptake inhibitor GBR 12909 and the presynaptic autoreceptor antagonist metoclopramide were used (along with SK&F 38393, quinpirole, and SCH 23390) in the present experiment. The effects of GBR 12909 on the amphetamine cue are not known. Metoclopramide has less affinity for the $D_2$ receptor than antagonists such as haloperidol but is about four times more efficacious at blocking the reinforcing properties of *d*-amphetamine than its affinity for $D_2$ receptors would predict (21). In addition, metoclopramide inhibits motor activity to a greater extent than sulpiride, which is also reported to antagonize the amphetamine cue (39), either because sulpiride penetrates the brain rather poorly or the two drugs act at different receptor populations (17).

## METHOD

### *Subjects*

Ten male, albino rats of Sprague-Dawley strain (Charles River Breeding Laboratories, Wilmington, MA), 90 days old at the beginning of training, were used. Animals were housed individually in a colony maintained on a 12 L : 12 D schedule (7:00 a.m.–7:00 p.m.) at a constant temperature (20–22°C) and humidity (39–50%). Initially, food and water were freely available but, after a 2-week habituation period, access to water was restricted to that available during training (on weekdays), a 10-min period (in home cages) after test sessions, and at least 12 h on weekends.

### *Apparatus*

Eight commercially available experimental chambers (BRS/LVE Model No. 143-23) contained in light- and sound-attenuating shells (BRS/LVE Model No. 132-04) were used for both training and testing. Each chamber contained a dipper mounted equidistant between two levers that delivered 0.1 ml water and a 28-V houselight that was illuminated to signal the onset of training or test sessions. Experimental events and data collection were controlled by an Apple IIe microcomputer located in an adjoining room.

### *Behavioral Procedures*

*Training.* Following deprivation of water for 23 h, the animals were injected IP with either 1.0 mg/kg *d*-amphetamine or 0.09% saline 15 min before being placed into the chambers. Half the rats ($n$ = 5) were trained to press the right lever to obtain water following *d*-amphetamine and the left lever following a comparable volume of saline; the lever associated with the two training conditions was reversed in the remaining animals. Responding on the incorrect lever was recorded but had no other consequences. *d*-Amphetamine or saline was given randomly, with the restriction that neither condition continue for more than 3 consecutive days. Initially, water reinforcers were provided after each correct response [fixed ratio (FR) 1]; however, as rates of lever pressing increased the ratio of correct responses required for reinforcement was raised gradually until all animals were responding under an FR 20 schedule. During this phase of the experiment, sessions were 29 min in duration and occurred 5 days per week.

Session length was then decreased to 20 min per day and training continued until performance under the FR 20 schedule stabilized. When all animals reached a criterion of 10 consecutive sessions in which the number of correct responses prior to the first reinforcer divided by the total number of responses ($\times$100) equaled or exceeded 80% correct, test sessions began.

*Testing.* During this phase of the experiment, animals were placed in the chambers as before but were given either different doses of the training drug (dose–responses tests), novel compounds (DA agonists) in place of the training drug (substitution or generalization tests), or a novel compound (DA antagonist) along with the training drug (combination test). All tests ended without reinforcement as soon as 20 responses on one or the other lever occurred or 20 min elapsed, whichever came first. Periodically, the accuracy of discrimination was assessed by exposing animals to the training drugs (saline or 1.0 mg/kg *d*-amphetamine) during *test* sessions. Dose–response, substitution, or combination tests were conducted once or twice per week on different days of the week in a random order providing animals maintained an accuracy of 80% correct for 3 consecutive training days.

### *Pharmacological Procedures*

The drugs used, injection–test intervals, and suppliers were: *d*-amphetamine sulfate (Sigma Chemical Co., St. Louis, MO); GBR 12909 [Research Biochemicals, Inc. (RBI), Natick, MA]; SK&F 38393 (RBI); Quinpirole (LY 171555) (Eli Lilly, Indianapolis, IN); SCH 23390, 29 min, SC (RBI); and metoclopramide HCL, 29 min (RBI). All drugs were given IP 15 min prior to testing unless otherwise noted; doses refer to the salts. All drugs were administered in 0.09% saline solution except GBR 12909, which was dissolved in deionized water acidified by adding three drops of 3 M glacial acetic acid per 20 ml solution.

### *Data Analysis*

Analysis of variance (ANOVA) followed by Scheffe's *F*-test were used to assess the data statistically. Substitution was defined as 80% or greater of the total number of responses during test sessions on the drug-appropriate lever *and* a significant difference between accuracies on drug and saline sessions. Incomplete substitution was defined as 60–80% response on the drug-appropriate lever. Antagonism of the *d*-amphetamine cue was defined as less than 39% response on the drug-appropriate lever *and* a significant difference between accuracies following the antagonist–training drug combination and the training drug alone; incomplete antagonism

TABLE 1

RESULTS OF SUBSTITUTION TESTS IN RATS TRAINED TO DISCRIMINATE d-AMPHETAMINE (AMP; 1 mg/kg) FROM SALINE

| Drug | Dose (mg/kg) | Percent* (±SEM) | Rate† (±SEM) | n/N‡ | F§ |
|---|---|---|---|---|---|
| d-Amphetamine | | | | | |
| AMP control | 1.0 | 99 ± 0 | 18 ± 5 | 10/10 | – |
| AMP | 0 | 5 ± 1 | 12 ± 2 | 10/10 | – |
| | 0.5 | 72 ± 1 | 8 ± 2 | 10/10 | 17.26¶ |
| | 1.0 | 99 ± 0 | 18 ± 5 | 10/10 | 34.9# |
| | 1.5 | 94 ± 3 | 6 ± 1 | 8/10 | 17.1# |
| | 2.0 | 96 ± 2 | 12 ± 2 | 9/10 | 32.29# |
| GBR 12909 | | | | | |
| AMP control | 1.0 | 99 ± 1 | 22 ± 5 | 10/10 | – |
| GBR 12909 | 0 | 5 ± 2 | 13 ± 2 | 10/10 | – |
| | 10.0 | 27 ± 11 | 40 ± 14 | 9/10 | 1.5 |
| | 15.0 | 68 ± 12 | 11 ± 4 | 9/10 | 6.1¶ |
| | 20.0 | 85 ± 11 | 16 ± 6 | 6/10 | 8.1# |
| SK&F 38393 | | | | | |
| AMP control | 1.0 | 99 ± 1 | 21 ± 6 | 8/8 | – |
| SK&F 38393 | 0 | 5 ± 2 | 13 ± 2 | 8/8 | – |
| | 1.0 | 2 ± 2 | 18 ± 7 | 8/8 | 0.17 |
| | 10.0 | 3 ± 2 | 18 ± 6 | 7/8 | 0.94 |
| Quinpirole (LY 171555) | | | | | |
| AMP control | 1.0 | 99 ± 1 | 16 ± 6 | 8/8 | – |
| Quinpirole | 0 | 5 ± 2 | 13 ± 2 | 8/8 | – |
| | 0.05 | 16 ± 5 | 13 ± 5 | 4/8 | 0.1 |
| | 0.075 | 2 ± 2 | 48 ± 1 | 7/8 | 0 |
| | 0.1 | 49 ± 15 | 2 ± 0 | 7/8 | 2.2¶ |
| | 0.2 | 50 ± 19 | 11 ± 0 | 7/8 | 2.3¶ |

*Percent of total number of responses occurring on the d-amphetamine-appropriate lever.
†Responses/min.
‡*n*, number of animals completing 20 responses; *N*, total number of animals tested.
§Result of Scheffe's *F*-test
¶Incomplete substitution (see text).
#Complete substitution (see text).

was defined as between 39 and 60% of the total number of responses occurring on the drug-appropriate lever *and* a significant difference between the antagonist-training drug combination and the training drug alone. Data from tests in which less than half the animals tested did not emit at least 20 responses were discarded.

## RESULTS

The d-amphetamine-saline discrimination was acquired within 29–55 days by all animals and maintained at an accuracy well above criterion; thus, the control values used in statistical tests were at or near 99% responding on the drug-appropriate lever following d-amphetamine and 5% responding on the drug-appropriate lever following saline (Tables 1 and 2).

The results obtained during substitution tests are shown in Table 1. In dose-response tests, 1.0–2.0 mg/kg d-amphetamine substituted completely for the training dose; 0.5 mg/kg substituted incompletely. When novel compounds were given in place of the training drug, only GBR 12909 substituted completely for d-amphetamine at a dose of 20 mg/kg and incompletely at a dose of 15 mg/kg (Table 1). Indeed, amount of responding on the d-amphetamine lever following this compound was monotonically related to dose. While 4 of the 10 animals tested were disrupted by GBR 12909, neither these nor any other effects on rate were statistically significant, perhaps because of the large variance in this measure of performance (Tables 1 and 2).

Neither SK&F 38393 nor LY 171555 substituted completely for 1 mg/kg d-amphetamine according to the criteria mentioned previously (Table 1). SK&F 38393 was so disruptive that the data with 7.5 and 10 mg/kg had to be discarded (because only two of the eight animals tested responded following the combination of these doses of SK&F 38393 and d-amphetamine); however, animals were given a second injection of 10 mg/kg SK&F 38393 and, while seven of the eight rats tested did respond sufficiently often to produce analyzable data, they pressed the drug-appropriate lever only 3% of the total number of times they responded.

Although the two higher doses of quinpirole (0.1 and 0.2 mg/kg) did engender amounts of responding on the drug-related level that differed significantly from those of saline controls (Table 1), this substitution was incomplete (no more than 50%).

Complete antagonism of the amphetamine cue was ob-

TABLE 2

RESULTS OF COMBINATION TESTS IN RATS TRAINED TO DISCRIMINATE *d*-AMPHETAMINE (AMP; 1 mg/kg) FROM SALINE

| Drug | Dose (mg/kg) | Percent* (±SEM) | Rate† (±SEM) | *n/N*‡ | *F*§ |
|---|---|---|---|---|---|
| Controls | | | | | |
| NaCl | – | 5 ± 2 | 13 ± 2 | 8/8 | – |
| AMP | 1.0 | 99 ± 1 | 21 ± 6 | 8/8 | – |
| Metoclopramide | 1.0 | 89 ± 8 | 23 ± 7 | 7/8 | 0.17 |
| | 2.0 | 76 ± 13 | 29 ± 9 | 8/8 | 0.96 |
| | 2.5 | 99 ± 1 | 29 ± 8 | 5/8 | 1.90 |
| | 5.0 | 88 ± 11 | 27 ± 13 | 7/8 | 0.22 |
| SCH 23390 | 0.02 | 52 ± 22 | 5 ± 1 | 2/8 | 1.40¶ |
| | 0.05 | 15 ± 7 | 8 ± 8 | 7/8 | 9.90# |
| | 0.075 | 79 ± 12 | 14 ± 16 | 8/8 | 0.61¶ |
| | 2.0 | 50 ± 20 | 0 | 4/8 | 2.40¶ |

*Percent of total number of responses occurring on the *d*-amphetamine-appropriate lever.

†Responses/min.

‡*n*, number of animals completing 20 responses; *N*, total number of animals tested.

§Result of Scheffe's *F*-test.

¶Incomplete substitution (see text).

#Complete substitution (see text).

tained with a dose of 0.05 mg/kg SCH 23390 but not at higher (or lower) doses (Table 2). At doses ranging from 1-5 mg/kg, metoclopramide failed to block the amphetamine cue.

## DISCUSSION

The most important result of the present experiment is the discovery that the *d*-amphetamine cue generalizes to compounds such as GBR 12909 that act selectively by inhibiting the uptake of DA (24). Thus, this mechanism could play an important role in the subjective effects of *d*-amphetamine as well as those of cocaine (above). However, the present results with GBR 12909 do not correspond completely to those reported previously; for example, Nielsen and Scheel-Krüger (39) found that, while the *d*-amphetamine cue generalizes to doses of GBR 12909 comparable to those used herein (15 mg/kg) amphetamine-like responding does *not* occur at higher doses of GBR 12909. However, the present data and those of Nielsen and Scheel-Krüger may be less discordant than they appear because they involve different time-response relationships: Nielsen and Scheel-Krüger injected (IP) 15 min before testing while we used an injection-test interval of 30 min; amphetamine transport reaches its peak approximately 40 min after IP injection (60).

Whatever differences may exist in the behavioral effects of *d*-amphetamine and cocaine (13) could be the result of the specific brain regions affected by the two compounds. While cocaine binds preferentially to DA transporter sites in mesolimbic areas such as the nucleus accumbens and the prefrontal cortex (34), low doses of *d*-amphetamine appear to act primarily in the striatum; higher doses are associated with the sequestration and consequential release of DA in mesolimbic as well as other regions of the brain (61).

In view of the fact that relatively nonselective DA agonists do not substitute reliably for CNS stimulants (above) and SK&F 38393 does not mimic *d*-amphetamine in either rats (16) or rhesus monkeys (59), the failure of SK&F 38393 to substitute completely for *d*-amphetamine in the present experiment could have been predicted. However, quinpirole has been reported to substitute for both *d*-amphetamine and cocaine in rats trained to discriminate stimulants from saline (9,17) although neither *d*-amphetamine nor cocaine mimics quinpirole in animals trained to discriminate this $D_1$ agonist from saline (3). Thus, taken together, the data suggest that activation of $D_1$ or $D_2$ receptors independently is not sufficient to evoke *d*-amphetamine- or cocaine-like responding (29,31,59). Nevertheless, it is interesting that quinpirole, like *d*-amphetamine, has been found to release DA (44) in addition to potently activating $D_2$ receptors (45).

Although low doses of *d*-amphetamine (e.g., 1.0 mg/kg) do not change cyclic adenosine monophosphate (cAMP) levels in either the striatum or mesolimbic DA system (37), such doses release enough DA to activate $D_1$ receptors; chronic amphetamine treatment may cause relatively high basal rates of DA release in the mesolimbic system that maintain $D_1$ receptor activity in a desensitized state. This, in turn, could result in lower basal and agonist-stimulated cAMP activity and, consequently, smaller agonist effects on this activity.

Although SK&F 38393 has many behavioral effects, some of these may originate from actions of this compound on the striatal DA system (51); given a desensitization in the mesolimbic system, SK&F 38393, a partial $D_1$ agonist, may not be sufficiently effective to mimic *d*-amphetamine. In addition, SK&F 38393 may desensitize $D_1$ receptors, because continuous exposure to this drug results in a failure to rotate in mice with striatal lesions (41,56). This desensitization could account for the difficulty in training rats to discriminate SK&F 38393. However, the fact that such desensitization does not occur when mice are given challenge doses of quinpirole argues against $D_1$-$D_2$ synergism (22). While by no means conclusive, there is also evidence that synergistic interactions occur at different DA receptor sites such that activation of $D_1$ receptors

may be necessary for the expression of effects mediated by $D_2$ receptors (6,12,47,48,53). Additional behavioral evidence of this hypothesis is provided by the fact that quinpirole-induced rotation, which has been blocked by SCH 23390, can be restored by SK&F 38393 (22).

Despite the behavioral studies that point to $D_1$–$D_2$ synergism, there is little evidence such a synergism occurs in drug discrimination experiments, although it has been reported that quinpirole potentiates the stimulus effects of SK&F 38393 in rat trained to discriminate SK&F 38393 from saline (54); however, in rats trained to discriminate quinpirole from saline SK&F 38393 does not potentiate the quinpirole cue (55).

The results of combination tests are often more consistent across different laboratories than those of generalization tests and are therefore more useful indicators of the neuronal substrates of the discriminable effects of psychoactive compounds (4). In the case of CNS stimulants, it has been mentioned that the stimulus properties of both *d*-amphetamine and cocaine are blocked by SCH 23390 and that the effects of *d*-amphetamine are blocked to a greater extent than those of cocaine by haloperidol. The results of the present experiment support these conclusions at least partially: SCH 23390 did attenuate the *d*-amphetamine cue *significantly*, although it did so over a narrow range of doses, perhaps because the selectivity of this compound as a $D_1$ antagonist decreases as a function of dose; even at reactively low doses, SCH 23390 has considerable affinity for 5-$HT_2$ receptors (11,37) and, at higher doses, inhibits the uptake of NE, DA, and 5-HT and binds to $D_2$ receptors (10). However, the failure of metoclopramide to block the *d*-amphetamine cue was unexpected because of its purported similarity to haloperidol in blocking other DA-mediated behaviors such as self-stimulation of the median forebrain bundle (1). However, although these $D_2$ antagonists may be equipotent in blocking pre-and postsynaptic DA receptors metoclopramide is more selective than haloperidol at presynaptic sites (38); unfortunately, the extent to which such selectivity is related to the actions of *d*-amphetamine in vivo is not known.

The dose of *d*-amphetamine used in training may be another factor contributing to the inability of metoclopramide to block the *d*-amphetamine cue. At low doses, psychomotor stimulants cause a decrease in locomotor activity similar to that seen after administration of antipsychotic drugs, a phenomenon attributed to the differential sensitivity of presynaptic autoreceptors (rather than postsynaptic DA receptors) to DA agonists (39). In addition, although metoclopramide is more selective for the presynaptic autoreceptor than haloperidol it does exhibit some affinity for 5-$HT_3$ (and perhaps other) receptors in the CNS (20); effects at this or any other of these sites could mask or attenuate its DA antagonist actions. The substituted benzamides as a class are also different from haloperidol in that they only increase DA turnover at doses high enough to attenuate apomorphine-induced stereotypies but not at doses that inhibit locomotor hyperactivity (35). The reason for this is not understood, but one explanation might be that hyperactivity and stereotypy induced by apomorphine is produced by activation of different subpopulations of $D_2$ receptors.

In conclusion, while further study is needed to determine the role of DA release and the effects of other (NE, 5-HT) receptor mechanisms on the stimulus properties of CNS stimulants the available data suggest that: a) The discriminable effects of *d*-amphetamine are due, at least in part, to inhibition of DA uptake; b) under the parameters of this experiment, stimulation of either $D_1$ receptors by the partial agonist SK&F 38393 or $D_2$ receptors by quinpirole is not sufficient to elicit an amphetamine-like cue; and c) blockade of $D_1$ receptors (by SCH 23390) may attenuate the subjective effects of 1.0 mg/kg *d*-amphetamine to a greater extent than blockade of presynaptic autoreceptors (by metoclopramide).

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