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Analysis of D_2 and D_3 Receptor-Selective Ligands in Rats Trained to Discriminate Cocaine from Saline

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GARNER, K. J. AND L. E. BAKER. *Analysis of D_2 and D_3 receptor-selective ligands in rats trained to discriminate cocaine from saline*. PHARMACOL BIOCHEM BEHAV **64**(2) 373–378, 1999.—This study examined the role of dopamine D_3 receptors in the stimulus generalization produced by 7-OH-DPAT and PD 128907 in rats trained to discriminate cocaine from saline. Twelve male Sprague–Dawley rats were trained to discriminate cocaine (10 mg/kg) from saline in a two-choice operant procedure using a FR20 schedule of water reinforcement. Stimulus generalization tests were administered with the D_3-preferring agonists (±)-7-OH-DPAT (0.01–0.3 mg/kg), (+)-7-OH-DPAT (0.01–0.3 mg/kg), and PD 128907 (0.01–0.3 mg/kg), and the selective D_2 agonist PNU-39156 (0.01–0.3 mg/kg). Complete generalization to cocaine was observed with (±)-7-OH-DPAT at doses that markedly suppressed response rate. Only partial stimulus generalization was observed with (+)-7-OH-DPAT and PD 128907 when these compounds were administered intraperitoneally, although subcutaneous injections of these compounds produced complete substitution. Response rate was also significantly reduced by these compounds. The selective D_2 agonist, PNU-91356 also fully substituted for the cocaine cue and suppressed response rate in a dose-dependent manner. To ascertain the importance of D_3 receptor actions in the stimulus generalization produced by (±)-7-OH-DPAT (0.1 mg/kg) and PD-128907 (0.3 mg/kg), the fairly selective D_3 antagonist, PNU-99194A (2.5–20 mg/kg) was also tested in combination with these compounds. Although PNU-99194A partially attenuated the stimulus generalization produced by (±)-7-OH-DPAT, it failed to block PD-128907 substitution for cocaine. These results indicate at least some involvement of D_3 receptors in the stimulus effects of (±)-7-OH-DPAT, although further investigations are clearly warranted. The present results also suggest that the cue properties of cocaine may be dissociated from the locomotor activating effects of this drug, because D_3/D_2 receptor agonists suppress locomotor activity but produce stimulus generalization to cocaine. © 1999 Elsevier Science Inc.

Cocaine D_2 Receptors D_3 Receptors 7-OH-DPAT PD 128907 PNU-93156 Drug discrimination

THE dopamine D_3 receptor has received considerable attention in recent investigations of the reinforcing and discriminative stimulus properties of cocaine. For example, the putative D_3 agonist, 7-hydroxy-*N*,*N*-di-n-propyl-2-aminotetralin (7-OH-DPAT) has been reported to shift the cocaine dose–response function to the left in animals trained to self-administer cocaine (8,22). Other researchers have noted that D_3-preferring antagonists reduce the breaking point in animals maintained on a progressive ratio of cocaine self-administration (25–27). These data suggest a potential modulatory role of the D_3 receptor in the reinforcing properties, and thereby, abuse liability of cocaine.

Presently, the role of D_3 receptors in cocaine's abuse potential remains highly speculative because D_3 receptor functions are not well understood. This is largely due to the lack of highly selective D_3 receptor ligands for investigation. However, several compounds have been reported to bind with moderate selectivity to D_3 over D_2 receptors. For instance, 7-OH-DPAT has been reported to have as much as a 100-fold greater affinity for D_3 over D_2 receptors (7,20), and PD 128907 has been reported to exhibit a 300-fold or greater D_3:D_2 selectivity (15,24).

Drug discrimination procedures are frequently employed to characterize novel compounds and investigate their receptor mechanisms. It is generally well established that drugs with similar pharmacological mechanisms exhibit generalization to one another in drug discrimination investigations. In an attempt to characterize the role of D_3 receptor mechanisms in the discriminative stimulus effects of psychostimulant drugs, a number of recent studies have examined the ef-

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fects of putative D_3 agonists in rats or monkeys trained to discriminate cocaine or *d*-amphetamine (1,4,6,19,28,30).

Several investigators have shown either complete or partial generalization to D_3-preferring agonists in rats trained to discriminate cocaine (1,19,28) or *d*-amphetamine (4,6). However, D_3-preferring antagonists [(+)-AJ76, (+)-UH232, (−)-DS121] have been reported to only partially attenuate the discrimination of cocaine (10,11) and the more selective D_3 antagonist PNU-99194A [5,6-di-methoxy-2-(dipropylamino)indan-hydrochloride] does not block cocaine discrimination (3,4). In a recent study, we reported that PNU-99194A also does not block the stimulus generalization produced by (+)-7-OH-DPAT in rats trained to discriminate *d*-amphetamine (4). These data question the importance of D_3 receptor modulation of the discriminative stimulus effects of (+)-7-OH-DPAT. Moreover, (+)-7-OH-DPAT failed to produce complete generalization for cocaine, indicating that D_2 receptors may also be important in mediating the cocaine cue (4). However, the training dose of cocaine is clearly an important determinant of stimulus generalization. Although we observed only partial substitution for 5 mg/kg cocaine (4), Acri et al. (1) reported complete substitution with (±)-7-OH-DPAT in rats trained to discriminate 10 mg/kg cocaine. The present study further evaluated D_3/D_2 agonists for stimulus generalization to 10 mg/kg cocaine.

Several researchers have investigated the role of D_2 receptors in the discriminative stimulus effects of cocaine in tests of substitution with a variety of agonists (5,9,17,29,32) and in combination tests with antagonists (2,5,9,12,13,17,21,32). The results of these studies have led to the general conclusion that D_2 receptor activation alone is not sufficient to produce cocaine-like discriminative stimulus effects (17,32). The development of more selective ligands for both D_2 and D_3 receptors may differentiate the functional roles of these receptors in the behavioral effects of cocaine. PNU-91356 [(R)-5,6-Dihydro-5-(propylamino)-4h-imidazo[4,5,1-ij]quinolin-2-(1H)-one, monohydrochloride] is a highly selective D_2 agonist (23). One aim of the present study was to examine this compound for stimulus generalization to cocaine and to compare its effects to those of the moderately selective D_3 agonists 7-OH-DPAT and PD 128907. In addition, this study further examined the ability of the highly selective D_3 antagonist PNU-99194A to block the stimulus generalization produced by (±)-7-OH-DPAT and PD 128907.

METHOD

Subjects

The subjects were 12 male Sprague–Dawley rats (Harlan Breeding Laboratories, Indianapolis, IN) aged 60–90 days and weighing 250–300 g at the beginning of the study. For the duration of the study, rats were housed individually in wire mesh cages, in a colony maintained on a 12 L:12 D cycle (0700 to 1900 h) and at a relatively constant temperature (20–22°C) and humidity (50–65%). Commercial rat feed was provided ad lib, and water was restricted to amounts received during 20-min training sessions and an additional 15 min per day. In addition, free access to water was given for 24 h approximately every 7 days. The animals were maintained in accordance with the general principles of animal husbandry outlined by the National Institutes of Health, and the experimental protocol was reviewed and approved by the Institutional Animal Care and Use Committee of Western Michigan University.

Apparatus

Training and testing sessions were conducted in eight standard operant chambers (MED Associates Inc., St. Albans, VT; ENV-001), housed in sound- and light-attenuating shells to provide ventilation and masking noise. Each chamber contained an overhead 28-V houselight and a liquid reinforcer delivery mechanism (0.1 ml) that was mounted equidistant between two levers on the front panel of the chamber. A Zenith 320-SX microcomputer programmed with MED-PC instrumentation and software (MED Associates Inc., St. Albans, VT; version 2.0) was used to control experimental events and data collection.

Drugs

(+)-7-OH-DPAT, PNU-91356, and PNU-99194A were generously provided by Pharmacia and Upjohn, Inc. (Kalamazoo, MI). Cocaine hydrochloride was provided by the National Institute on Drug Abuse (Rockville, MD). (±)-7-OH-DPAT and PD 128907 were purchased from Research Biochemicals International (Natick, MA). All drugs were dissolved in sterile bacteriostatic 0.90% saline. Cocaine was administered intraperitoneally (IP). (±)-7-OH-DPAT and PNU-99194A were administered subcutaneously (SC). (+)-7-OH-DPAT, PD 128907 and PNU-91356 were administered by both IP and SC injection. All doses of each drug were calculated based on the salt.

Training Procedures

Twelve rats were trained to discriminate cocaine (10.0 mg/kg, IP) from saline using a two-lever operant task under a fixed-ratio 20 (FR20) schedule of water reinforcement. Drug or saline injections were administered 15 min prior to the beginning of training sessions. Half the animals in each training group were reinforced with water (0.1 ml) for responding on the right lever after drug injections and on the left lever after saline injections. Conditions were reversed for the remaining animals. Levers were wiped with isopropyl alcohol before each session to reduce the influence of olfactory stimuli on lever pressing (16).

Training sessions lasted for 20 min, and were conducted 6 days per week. Drug and saline injections were given in a pseudorandom order, with the limitation that no more than two consecutive sessions occurred under the same condition. Training under each condition began on a FR1 schedule. Once responding was stable, the number of consecutive correct responses required for reinforcement was gradually increased until the final FR20 was reached. The criterion for discrimination was set at a minimum of 80% correct-lever selection prior to the delivery of the first reinforcer for 10 consecutive training sessions. Each subject was required to meet this criterion before testing began.

Testing Procedures

Stimulus generalization tests were conducted with several doses of cocaine (0, 2.5, 5.0, and 10.0 mg/kg), the D_3-preferring agonists, (+)-7-OH-DPAT (0.01, 0.03, 0.10, and 0.30 mg/kg), (±)-7-OH-DPAT (0.01, 0.03, 0.10, and 0.30 mg/kg), and PD 128907 (0.01, 0.03, 0.10, and 0.30 mg/kg), and the D_2-selective agonist, PNU-91356 (0.01, 0.03, 0.10, and 0.30 mg/kg). For stimulus generalization tests, all injections were administered 15 min prior to test sessions. Additionally, the D_3-preferring antagonist PNU-99194A (2.5, 5.0, 10.0, and 20.0 mg/kg, SC, 30 min) was administered in combination with (±)-7-OH-DPAT (0.1 mg/kg SC, 15 min) and in combination PD-128907 (0.3

mg/kg SC, 15 min). Test sessions were conducted in a similar manner to training session with the exception that no reinforcers were delivered and each animal was removed from the chamber upon completion of 20 consecutive responses on either lever or when 20 min elapsed, whichever occurred first. For each drug tested, the order of doses was counterbalanced among subjects, and half the animals received tests after drug maintenance sessions while the other half received tests after saline maintenance sessions. Subjects were administered at least two training sessions between test sessions, and were required to maintain the 80% criterion under both training conditions before each test.

Data Analysis

Dose–response data were presented as the percent of total responses made on the drug-appropriate lever during test sessions. Response rate was presented as the number of responses made (on either lever) per second during test sessions. For each dose tested, the mean and SEM were calculated for each of these dependent measures. In the event that an animal did not complete at least 15 total responses during a test session, the percentage of drug-lever responses for that test was not included in the statistical analyses. Drug-lever selection that was 80% or greater was considered evidence for stimulus generalization. Drug-appropriate responding between 20 and 80% was considered evidence for partial substitution. For drugs that produced stimulus generalization, the dose–response curve was also analyzed using a nonlinear regression, and ED_{50}s and confidence intervals were calculated. One-way analyses of variance were conducted on response rate data. Statistical analyses were conducted using the software GraphPad Prism (GraphPad, Inc., San Diego, CA).

RESULTS

All subjects met the discrimination criterion stated above. The mean number of sessions to criterion was 54.67 (SEM = 4.11, range: 37–79). After meeting the initial criterion for discrimination, four animals began to exhibit poor stimulus control due to equipment failure. After the equipment problem was fixed, these animals were required to meet the discrimination criterion (10 consecutive sessions above 80% correct lever selection prior to first reinforcer) again before they were administered test sessions.

The cocaine dose–response curve and results of stimulus generalization tests are displayed in Fig. 1. The ED_{50} for cocaine was 1.34 mg/kg (95% confidence intervals: 0.36–4.93 mg/kg). (±)-7-OH-DPAT substituted for cocaine in a dose-dependent manner (ED_{50} = 0.02 mg/kg; 95% confidence intervals: 0.006–0.09 mg/kg). This compound also dose dependently reduced response rate, and this effect was statistically significant, $F(3, 47) = 6.11$, $p < 0.05$. Both 0.1 and 0.3 mg/kg produced complete stimulus generalization and reduced response rate significantly below saline control levels ($p < 0.01$). Eight of the 12 animals tested at 0.1 mg/kg completed the response requirement, and all eight exhibited complete stimulus generalization. Seven of the 12 animals tested at 0.3 mg/kg completed the response requirement, and six of these animals exhibited complete stimulus generalization.

(+)-7-OH-DPAT (IP) also produced dose-dependent increases in drug-appropriate responding; however, this compound produced only partial substitution at 0.3 mg/kg. Higher doses were not examined because eight of the 12 animals produced six or fewer responses when tested at this dose. Of the four animals that did complete the FR requirement, three exhibited complete stimulus generalization. The response rate suppression produced by (+)-7-OH-DPAT was statistically significant, $F(4, 59) = 6.72$, $p < 0.001$. Subjects were also tested with two doses of this compound (0.1 and 0.3 mg/kg) following SC injection (see Fig. 1C). Of the 10 animals that

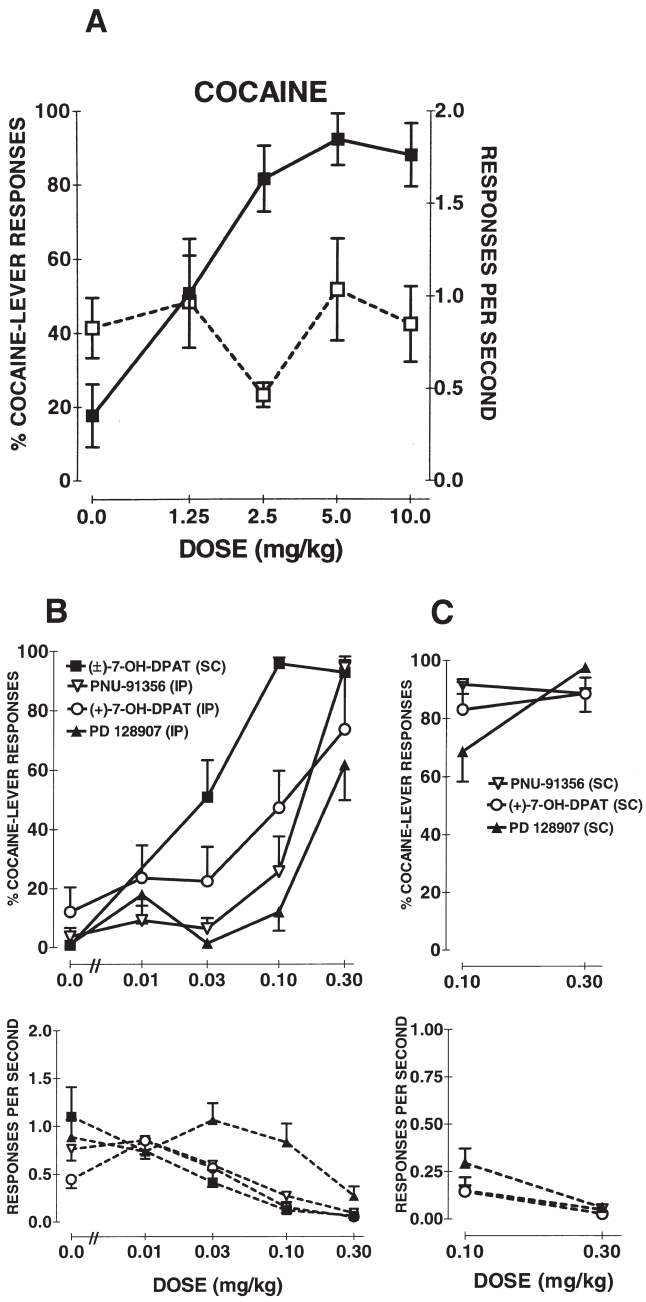

FIG. 1. (A) Cocaine dose–response curve: percent cocaine-lever responses and response rate (n = 12). (B) Results of stimulus generalization tests with (±)-7-OH-DPAT, (+)-7-OH-DPAT, PD 128907, and PNU-91356 in rats trained to discriminate cocaine (10 mg/kg) from saline (n = 12). (C) Results of stimulus generalization tests with (+)-7-OH-DPAT (n = 12), PD 128907 (n = 11), and PNU-91356 (n = 11) following SC injection. In B and C, the percentage of cocaine-lever responses is indicated in the top graph, and response rate is indicated in the bottom graph. See text for details regarding the number of animals that completed the response requirements during tests.

completed the FR requirement, nine exhibited complete stimulus generalization following administration of the 0.1 mg/kg dose of (+)-7-OH-DPAT. Five animals completed the FR requirement following SC administration of 0.3 mg/kg, and four of these animals exhibited complete stimulus generalization.

When administered IP, PD 128907 also produced only partial substitution for cocaine. Ten animals completed at least 20 responses during substitution tests with 0.3 mg/kg. Two of these animals emitted 0% drug-appropriate responses, four animals emitted between 45 and 70% drug-appropriate responses, and four animals emitted greater than 90% drug-appropriate responses. Ten animals were also administered SC injections of PD 128907 (0.1 and 0.3 mg/kg). Nine animals completed the response requirement following the 0.3 mg/kg dose, and all nine exhibited complete generalization. This compound also significantly reduced response rate, $F(4, 59) = 3.75$, $p < 0.01$.

The selective D_2 agonist, PNU-91356, produced dose-dependent increases in drug-appropriate responding and produced complete substitution for cocaine when administered IP ($ED_{50} = 0.16$ mg/kg). Nine animals completed the response requirement following 0.3 mg/kg, and all nine exhibited complete stimulus generalization at this dose. Subcutaneous injections of this compound also produced complete substitution at both 0.1 and 0.3 mg/kg, although only five animals completed the response requirement following 0.3 mg/kg (SC). This compound also produced statistically significant response rate suppression, $F(4, 59) = 6.47$, $p < 0.001$.

Figure 2 depicts the effects of PNU-99194A on the stimulus generalization produced by (±)-7-OH-DPAT (0.1 mg/kg) and PD-128907 (.03 mg/kg). this D_3-preferring antagonist did not block the substitution of PD-128907, and only partially blocked the substitution of (±)-7-OH-DPAT. This partial antagonism only occurred at the highest dose of PNU-99194A. Of the six animals that completed the response requirement during tests with 20 mg/kg PNU-99194A and (±)-7-OH-DPAT, four emitted between 25 and 70% of their responses on the cocaine-appropriate lever, and two exhibited greater than 90% drug-appropriate responding. Three of the six animals administered 20 mg/kg PNU-99194A with PD-128907 were severely disrupted and made no responses. Thus, higher doses of PNU-99194A were not examined in combination with PD-128907.

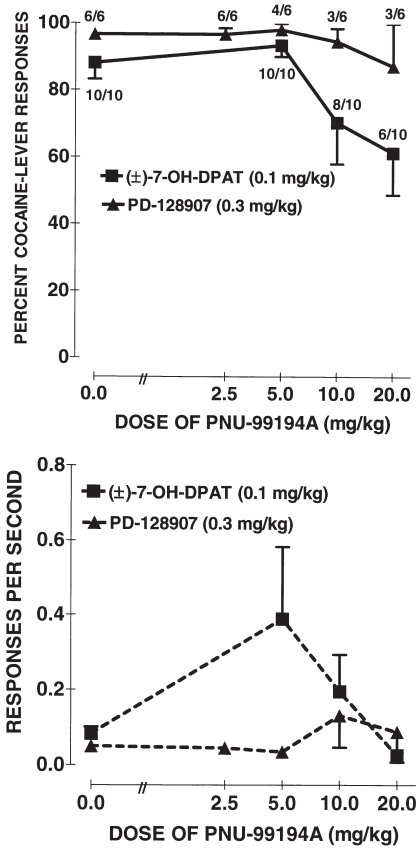

FIG. 2. Effects of PNU-99194A on the stimulus generalization produced by (±)-7-OH-DPAT (0.1 mg/kg SC; $n = 10$) or PD 128907 (0.3 mg/kg SC, $n = 6$) in rats trained to discriminate cocaine (10 mg/kg) from saline. The percentage of cocaine-lever responses is indicated in the top graph, and response rate is indicated in the bottom graph. The number of animals that completed the response requirement and the number of animals that were tested at each dose are represented in the figure as *n/N*.

DISCUSSION

The results of this study support previous findings that moderately selective dopamine D_3 receptor agonists produce stimulus generalization in rats trained to discriminate cocaine. As noted by Acri et al. (1), complete substitution occurs at doses that severely disrupt responding. The present results demonstrated only partial substitution for cocaine with PD 128907 and (+)-7-OH-DPAT when these compounds were administered by IP injection. However, the two highest doses (0.1 and 0.3 mg/kg) were also tested following SC injection, and evidence for complete stimulus generalization was observed. This is likely due to better drug absorption via the SC route. The racemic mixture of 7-OH-DPAT was also administered by SC injection, and produced full substitution for cocaine.

The present results suggest that the stimulus properties of cocaine may be disassociated from the locomotor activation produced by this drug. As mentioned above, the D_3/D_2 agonists markedly reduced response rates in the present study. Observations of the animals following administration of higher doses indicated sedative effects and a general decline in activity. This is consistent with previous reports that both 7-OH-DPAT and PD 128907 reduce locomotor activity in rats (14). In contrast, D_3 antagonists have been noted to produce locomotor activation, especially in rats habituated to their surroundings (18,31). Previous studies clearly indicate that D_3 antagonists do not mimic cocaine's discriminative stimulus effects (3,4,10,11).

The highly selective D_2 agonist, PNU-91356 also exhibited full substitution for cocaine in the present study. Following IP administration, this compound exhibited more complete substitution than either (+)-7-OH-DPAT or PD 128907 at an equivalent dose. Former research with other D_2 receptor agonists in tests of stimulus generalization to cocaine have provided inconsistent findings. For example, some investigators reported complete substitution with quinpirole in rats (5,9), while others reported only partial substitution with this compound and a variety of other D_2 selective agonists (32). Additionally, quinpirole did not substitute for cocaine in monkeys (17). Investigations of D_2 antagonists on cocaine discrimination have also produced some inconsistent findings. Although several researchers have reported that the D_2 antagonist haloperidol fails to completely block the discriminative stimulus

effects of cocaine (2,5,12,13,21,32), others have observed haloperidol to block the cocaine cue (9,17).

Despite these somewhat equivocal results, it has been suggested that D_2 receptor activation alone is insufficient to produce cocaine-like discriminative stimulus effects (17,32). However, with the development of more selective D_2 receptor ligands, the role of D_2 receptor actions in cocaine's discriminative stimulus effects warrants further investigation. Although previously considered a relatively selective D_2 agonist, quinpirole has an equivalent binding affinity for D_2 and D_3 receptors (23). Furthermore, although the agonists 7-OH-DPAT and PD 128907 bind with moderate selectivity to D_3 receptors, they also have relatively high affinities for D_2 receptors. Thus, the specific role of D_2 vs. D_3 receptors in the cocaine-like discriminative stimulus effects observed with these compounds (1) are still unclear.

The present study attempted to differentiate the relative importance of D_2 vs. D_3 receptors in the discriminative stimulus effects of cocaine by 1) comparing a highly selective D_2 agonist to moderately selective D_3 agonists, and 2) by challenging the substitution of (±)-7-OH-DPAT and PD 128907 for cocaine with a D_3 antagonist. PNU-91356 has an approximately 30-fold higher K_i for D_2 receptors than for D_3 receptors (23). Thus, the present results suggest that selective D_2 receptor activation may be sufficient to produce cocaine-like discriminative stimulus effects. However, investigations utilizing selective D_3 antagonists to challenge the substitution of D_3/D_2 agonists for cocaine are required to confirm this conclusion. Recent investigations by Spealman (28) examined the substitution of PD 128907 for cocaine in monkeys, then assessed three D_2 antagonists (nemonapride, eticlopride, and YM-43611) with differing affinities for D_3 receptors in combination with PD 128907. He reported that the order of potency with which these antagonists attenuated the substitution of PD 128907 for cocaine corresponded to the order of affinity of these compounds at cloned human D_3 receptors. Other researchers have also assessed the effects of eticlopride on the stimulus generalization produced by (±)-7-OH-DPAT in rats trained to discriminate *d*-amphetamine, and reported that (±)-7-OH-DPAT substitution was partially blocked by this D_2/D_3 antagonist (6).

Previous investigations from our laboratory (4) indicated that the relatively selective D_3 antagonist PNU-99194A does not block (+)-7-OH-DPAT substitution for cocaine (5 mg/kg) or *d*-amphetamine (1 mg/kg). However, the present findings demonstrate partial antagonism of (±)-7-OH-DPAT substitution for cocaine (10 mg/kg). These results suggest at least some involvement of D_3 receptors in modulating the discriminative stimulus effects of (±)-7-OH-DPAT. It is intriguing, though, that PNU-99194A failed to block the substitution of PD-128907, which is reported to have a greater D_3 receptor affinity than (±)-7-OH-DPAT (15,24). Clearly, additional investigations are warranted. To investigate the importance of D_2 receptors in the stimulus effects of these D_3/D_2 agonists, we are also currently investigating the highly selective D_2 antagonist, remoxipride, for blockade of PD-128907 and (±)-7-OH-DPAT substitution. Preliminary data suggest that remoxipride (0.1–3.0 mg/kg) does not antagonize the stimulus generalization produced by these compounds. In addition, to further examine the role of D_3 receptors in mediating the discriminative stimulus effects of 7-OH-DPAT, we are also currently testing the effects of PNU-99194A in rats trained to discriminate the (+)-isomer of this compound. Preliminary findings also indicate partial antagonism of the (+)-7-OH-DPAT cue by PNU-99194A.

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REFERENCES

1. Acri, J. B.; Carter, S.; Alling, K.; Geter-Douglass, B.; Dijkstra, D.; Wikstrom, H.; Katz, J.; Witkin, J.: Assessment of cocaine-like discriminative stimulus effects of dopamine D_3 receptor ligands. Eur. J. Pharmacol. 281:R7–R9; 1995.
2. Baker, L. E.; Riddle, E. E.; Saunders, R. B.; Appel, J. B.: The role of monoamine uptake in the discriminative stimulus effects of cocaine and related compounds. Behav. Pharmacol 4:69–79; 1993.
3. Baker, L. E.; Miller, M. E.; Svensson, K.: Assessment of the discriminative stimulus effects of the selective dopamine D_3 antagonist PNU-99194A in rats: Comparison to psychostimulants. Behav. Pharmacol. 8:243–252; 1997.
4. Baker, L. E.; Svensson, K. A.; Garner, K. J.; Goodwin, A. K.: The dopamine receptor antagonist PNU-99194A fails to block (+)-7-OH-DPAT substitution for *d*-amphetamine or cocaine. Eur. J. Pharmacol. 358:101–109; 1998.
5. Barrett, R. L.; Appel, J. B.: Effects of stimulation and blockade of dopamine receptor subtypes on the discriminative stimulus properties of cocaine. Psychopharmacology (Berlin) 99:13–16; 1989.
6. Bevens, R. A.; Klebaur, J. E.; Bardo, M. T.: 7-OH-DPAT has *d*-amphetamine-like discriminative stimulus properties. Pharmacol. Biochem. Behav. 58:485–490; 1997.
7. Burris, K. D.; Pacheco, M. A.; Filtz, T. M.; Kung, M.-P.; Kung, H. F.; Molinoff, P. B.: Lack of discrimination by agonists for D_2 and D_3 dopamine receptors. Neuropsychopharmacology 12:335–345; 1995.
8. Caine, S. B.; Koob, G. F.: Pretreatment with the dopamine agonist 7-OH-DPAT shifts the cocaine self-administration dose–effect function to the left under different schedules in the rat. Behav. Pharmacol. 6:333–347; 1995.
9. Callahan, P. M.; Cunningham, K. A.: Discriminative stimulus properties of cocaine in relation to dopamine D_2 receptor function in rats. J. Pharmacol. Exp. Ther. 266:585–592; 1993.
10. Callahan, P. M.; Piercey, M. F.; Cunningham, K. A.: Effects of putative dopamine autoreceptor antagonists (+)-AJ 76 and (+)-UH 232 on the discriminative stimulus properties of cocaine. Psychopharmacology (Berlin) 107:73–77; 1992.
11. Clark, D.; Exner, M.; Furmidge, L. J.; Svensson, K.; Sonesson, C.: Effects of the dopamine autoreceptor antagonist (−)-DS 121 on the discriminative stimulus properties of *d*-amphetamine and cocaine. Eur. J. Pharmacol. 275:67–74; 1995.
12. Colpaert, F. C.; Niemegeers, C. J. E.; Janssen, P. A. J.: Neuroleptic interference with the cocaine cue: Internal stimulus control of behavior and psychosis. Psychopharmacology (Berlin) 58:247–255; 1978.
13. Colpaert, F. C.; Niemegeers, C. J. E.; Janssen, P. A. J.: Discriminative stimulus properties of cocaine and *d*-amphetamine and antagonism by haloperidol: A comparative study. Neuropharmacology 17:937–942; 1978.
14. Daly, S. A.; Waddington, J. L.: Behavioural effects of the putative D-3 dopamine receptor agonist 7-OH-DPAT in relation to other "D-2-like" agonists. Neuropharmacology 32:509–510; 1993.

15. DeMattos, S. B.; Pugsley, T. A.; Shih, Y. S.; Whetzel, S. Z.; Georgic, L. M.; VanLeeuwen, D. H.; MacKenzie, R. G.; Smith, S. J.; Glase, S. A.; Wise, L. D.; Heffener, T. G.: Identification and characterization of a dopamine D_3 selective compound, PD 128907. Soc. Neurosci. Abstr. 19:77; 1993.
16. Extance, K.; Goudie, A. J.: Inter-animal olfactory cues in operant drug discrimination procedures in rat. Psychopharmacology (Berlin) 91:67–73; 1981.
17. Kleven, M. S.; Anthony, E. W.; Woolverton, W. L.: Pharmacological characterization of the discriminative stimulus effects of cocaine in rhesus monkeys. J. Pharmacol. Exp. Ther. 254:312–317; 1990.
18. Kling-Petersen, T.; Ljung, E.; Wollter, L.; Svensson, K.: Effects of the dopamine D3- and autoreceptor preferring antagonist (−)-DS 121 on locomotor activity, conditioned place preference and intracranial self-stimulation in the rat. Behav. Pharmacol. 6:107–115; 1995.
19. Lamas, X.; Negus, S. S.; Nader, M. A.; Mello, N. K.: Effects of the putative dopamine D3 receptor agonist 7-OH-DPAT in rhesus monkeys trained to discriminate cocaine from saline. Psychopharmacology (Berlin) 124:306–314; 1996.
20. Levesque, D.; Diaz, J.; Pilon, C.; Martres, M.; Giros, B.; Souil, E.; Schott, D.; Morgat, J.; Schwartz, J.; Sokolof, P.: Identification, characterization and localization of the dopamine D_3 receptor in rat brain using 7-[3H]-hydroxy-N,N-di-n-propyl-2-aminotetralin. Proc. Natl. Acad. Sci. USA 89:8155–8159; 1992.
21. McKenna, M. L.; Ho, B. T.: The role of dopamine in the discriminative stimulus properties of cocaine. Neuropharmacology 19:297–303; 1980.
22. Parsons, L. H.; Caine, S. B.; Sokolof, P.; Schwartz, J. C.; Koob, G. F.; Weiss, F.: Neurochemical evidence that postsynaptic nucleus accumbens D-3 receptor stimulation enhances cocaine reinforcement. J. Neurochem. 3:1078–1089; 1996.
23. Piercey, M. F.; Camacho-Ochoa, M.; Smith, M. W.: Functional roles for dopamine receptor subtypes. Clin. Neuropharmacol. 18:S34–S42; 1995.
24. Pugsley, T. A.; Davis, M. D.; Akunne, H. C.; MacKenzie, R. G.; Shih, Y. H.; Damsma, G.; Wikstrom, H.; Whetzel, S. Z.; Georgic, L. M.; Cooke, L. W.; DeMattos, S. B.; Corbin, A. E.; Glase, S. A.; Wise, L. D.; Dijkstra, D.; Heffner, T. G.: Neurochemical and functional characterization of the preferentially selective D_3 agonist PD 128907. J. Pharmacol. Exp. Ther. 275:1355–1366; 1995.
25. Richardson, N. R.; Piercey, M. F.; Svensson, K.; Collins, R. J.; Myers, J. E.; Roberts, D. C. S.: Antagonism of cocaine self-administration by the preferential dopamine autoreceptor antagonist, (+)-AJ 76. Brain Res. 619:15–21; 1993.
26. Roberts, D. C. S.; Ranaldi, R.: Effect of dopaminergic drugs on cocaine reinforcement. Clin. Neuropharmacol. 18:S84–S95; 1995.
27. Smith, A.; Piercey, M. F.; Roberts, D. C. S.: Effects of (−)DS 121 and (+)-UH 232 on cocaine self-administration in rats. Psychopharmacology (Berlin) 120:93–98; 1995.
28. Spealman, R. D.: Dopamine D_3 receptor agonists partially reproduce the discriminative stimulus effects of cocaine in squirrel monkey. J. Pharmacol. Exp. Ther. 278:1128–1137; 1996.
29. Spealman, R. D.; Bergman, J.; Madras, B. K.; Melia, K. F.: Discriminative stimulus effects of cocaine in squirrel monkeys: Involvement of dopamine receptor subtypes. J. Pharmacol. Exp. Ther. 258:945–953; 1991.
30. Varty, G. B.; Higgins, G. A.: Investigations into the nature of a 7-OH-DPAT discriminative cue: Comparison with *d*-amphetamine. Eur. J. Pharmacol. 339:101–107; 1997.
31. Waters, N.; Svensson, K.; Haadsma-Svenson, S. R.; Smith, M. W.; Carlsson, A.: The dopamine D_3-receptor: A postsynaptic receptor inhibitory of rat locomotor activity. J. Neural Transm. 94:11–19; 1993.
32. Witkin, J. M.; Nichols, D. E.; Terry, P.; Katz, J. L.: Behavioral effects of selective dopaminergic compounds in rats discriminating cocaine injections. J. Pharmacol. Exp. Ther. 257:706–713; 1991.