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Reevaluation of PNU-99194A discriminative stimulus effects Potentiation by both a D_2 antagonist and a D_3/D_2 agonist

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Abstract

This study evaluated the relative importance of D_3 receptor antagonism in the discriminative stimulus effects of the putative D_3 receptor antagonist PNU-99194A. Eight male Sprague–Dawley rats were trained to discriminate PNU-99194A (10 mg/kg sc) from vehicle in a two-choice drug discrimination procedure under a FR 20 schedule of food reinforcement. The selective D_3 antagonists PD 152255 and S14297 were examined for stimulus generalization. The D_2 antagonist haloperidol and the D_2/D_3 receptor agonist (+)-7-OH-DPAT were also assessed for antagonism of PNU-99194A discrimination. PD 152255 (1.0–3.0 mg/kg) engendered no generalization to PNU-99194A. Due to its markedly rate-suppressive effects, PD 152255 could not be tested at higher doses. S-14297 produced partial substitution (66%) for PNU-99194A at both 3.0 and 8.0 mg/kg. Neither haloperidol nor (+)-7-OH-DPAT blocked the discrimination of PNU-99194A and, surprisingly, actually appeared to potentiate its effects. These data, along with other recent findings, suggest that the discriminative stimulus effects of PNU-99194A appear to involve complex pharmacological actions and are not solely mediated by D_3 receptor antagonism.

Keywords: PNU-99194A; 7-OH-DPAT; S-14297; PD 152255; D_3 receptors; Drug discrimination; Rats

1. Introduction

Because the D_3 dopamine (DA) receptor is concentrated in terminal regions of the mesolimbic DA system (Sokoloff et al., 1990) and exhibits a high affinity for a number of antipsychotic drugs (Bristow et al., 1998; Levesque et al., 1992; Freedman et al., 1994), the functional significance of this receptor subtype has been a topic of considerable research interest for the last decade. Until recently, the lack of selective tools for examining D_3 receptor-mediated functions has hindered scientific progress. Recent reports of highly selective D_3 receptor antagonists (e.g., S14297, S33084 and PD 152255) hold promise for more extensive evaluations of D_3-mediated actions in vivo. Prior to the development of these compounds, PNU-99194A (5,6-methoxy-2-(dipropylamino) indan-hydrochloride) was considered one of the most selective D_3 receptor antagonists available for experimental investigation. This compound binds with nanomolar potency to the D_3 receptor subtype and displays a 20-fold lower potency at the D_2 receptor in vitro (Haadsma-Svensson and Svensson, 1998).

PNU-99194A increases locomotor activity at doses that do not significantly increase DA release in the rat striatum or nucleus accumbens (Waters et al., 1993). Moreover, this compound readily acquires discriminative stimulus control in rats (Baker et al., 1997; Franklin et al., 1998; Goudie et al., 2001). We have previously reported that rats trained to discriminate PNU-99194A do not generalize to psychostimulant drugs (Baker et al., 1997) or DA agonists with various receptor selectivities (Franklin et al., 1998). Other D_3-preferring antagonists ((+)-AJ-76, (−)-DS 121 and (+)-UH-232) reliably substitute for the PNU-99194A-cue (Franklin et al., 1998; Goudie et al., 2001), and therefore D_3 receptor antagonism was hypothesized as critically important in maintaining PNU-99194A's discriminative stimulus effects. However, these antagonists exhibit a substantially lower selectivity for D_3 versus D_2 sites compared to more recently developed compounds, such as S-14297 and PD 152255. Moreover, we recently reported that the atypical antipsy-

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chotic clozapine and the antimuscarinic compounds, scopolamine and trihexyphenidyl, also exhibit stimulus generalization for PNU-99194A (Goudie et al., 2001). These findings suggest that antimuscarinic actions may contribute to PNU-99194A's discriminative stimulus effects and might account for the PNU-99194A substitution observed by the atypical antipsychotic clozapine due to clozapine's nanomolar potency for the muscarinic M_1 receptor (Bymaster et al., 1996). However, because PNU-99194A has only a weak affinity for muscarinic receptors (Audinot et al., 1998; Goudie et al., 2001), there is little support for this alternative hypothesis.

While PNU-99194A and clozapine do appear to produce similar discriminative stimulus effects, the pharmacological mechanisms underlying these similarities remain to be determined. A specific aim of this study was to further examine the relative importance of D_3 receptor antagonism in PNU-99194A's discriminative stimulus effects by assessing other selective D_3 antagonists for stimulus generalization. PD 152255 (*E*-1,1′-(2-butene-1,4-diyl)bis[2-[4-[3-(1-piperidinyl)propoxy]-phenyl]-1*H*-benzimidazole) displays a 45-fold preference for D_3 over D_2 DA receptors as an antagonist in vitro and, like PNU-99194A, PD 152255 increases locomotor activity in acclimated rats (Corbin et al., 1998). S-14297 ((+)-[7-(*N*,*N*-dipropylamino)-5,6,7,8-tetrahydro-naphtho-(2,3*b*)-dihydro,2,3-furane]) also exhibits a nanomolar affinity for D_3 receptors and prevents (+)-7-OH-DPAT-induced hypothermia (Millan et al., 1995; Audinot et al., 1998). In drug discrimination assays, PD 152255 and S-14297 did not produce stimulus generalization to clozapine (Goudie et al., 2001). Characterization of these compounds in animals trained to discriminate PNU-99194A may further elucidate the relative importance of PNU-99194A D_3 receptor mediation.

Additionally, the D_2 antagonist haloperidol and the D_3/D_2 agonist (+)-7-OH-DPAT were examined for blockade of PNU-99194A's discriminative stimulus effects. While this study was in progress, Depoortere et al. (2000) published a report indicating that PNU-99194A potentiated the discriminative stimulus effects of 7-OH-DPAT. That study examined a single dose of PNU-99194A (10.0 mg/kg) in combination with each of four 7-OH-DPAT doses and illustrated a leftward shift in the 7-OH-DPAT dose response function. The current study complements those findings.

2. Methods

2.1. Subjects

Subjects consisted of eight male Sprague–Dawley rats (Harlan Breeding Laboratories, Indianapolis, IN). These animals were 50–60 days old and weighed 200–250 g at the beginning of the study. All rats were housed in plastic hanging cages (18.5×24×38 cm) and maintained at 85% of free-feeding weights with free access to water. The animal colony was maintained on a 12-h light/dark cycle and consistent room temperature (20–22 °C). All animals were maintained in accordance with the general principles of animal husbandry outlined by the National Institutes of Health and the experimental protocols were approved by the Institutional Animal Care and Use Committee of Western Michigan University.

2.2. Apparatus

Training and testing sessions were conducted in eight standard operant chambers (MED Associates, Georgia, VT), housed in sound- and light-attenuating shells equipped with fans to provide ventilation and masking noise. Eight chambers contained an overhead 28-V houselight, three retractable levers and a food pellet dispenser located above the center lever location. The center lever was used only during the initial autoshaping sessions. MED-PC instrumentation and software (MED Associates) controlled experimental events and data collection.

2.3. Drugs

PNU-99194A-hydrochloride (Pharmacia, Kalamazoo, MI) was dissolved in sterile deionized water and administered by subcutaneous injection. S-14297 (Institut de Recherches Servier, Paris, France) was dissolved in a few drops of lactic acid, diluted with sterilized water and administered subcutaneously. PD 152255 (Parke-Davis, Ann Arbor, MI) and haloperidol (Sigma, St. Louis, MO) were dissolved in 0.1 N HCl and administered intraperitoneally. (+)-7-OH-DPAT (Pharmacia) was dissolved in sterile bacteriostatic 0.90% saline and administered subcutaneously.

2.4. Discrimination training procedures

All subjects were initially exposed to a fixed time 60-s schedule of food delivery with no levers present for a single 1-h training session. Subsequently, rats were trained to lever press on a center lever under a fixed ratio 1 (FR 1) schedule of reinforcement for one session. Once lever-pressing behavior was reliably maintained, discrimination training began.

PNU-99194A (10 mg/kg sc) or vehicle injections were administered 15 min prior to the beginning of training sessions. Initial training sessions began under a FR 1 schedule and the FR value was gradually incremented until responding was reliably maintained on a FR 20 resetting schedule, in which 20 consecutive responses on the condition-appropriate lever were required for reinforcement. Half the animals were reinforced with 45 mg Bioserv (Frenchtown, NJ) food pellets for responding on the right lever after drug injections and on the left lever after vehicle injections. Conditions were reversed for the remaining animals. Training sessions lasted 20 min and were conducted 5–6 days/week. Drug and vehicle injections were given in a pseudo-random order, with the limitation that no

more than two consecutive sessions occurred under the same condition. Levers were wiped with isopropyl alcohol before each session to reduce the influence of olfactory stimuli on lever pressing (Extance and Goudie, 1981). The criterion for discrimination was a minimum of 80% correct-lever selection prior to the delivery of the first reinforcer and during the remainder of the session for at least 9 of 10 consecutive training sessions.

2.5. Testing procedures

Stimulus generalization tests were initiated as each subject met the criterion stated above. Test sessions were conducted in a similar manner to training sessions with the exception that no reinforcers were delivered and the 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 test compounds on a day after a drug session, while the other half were tested after a vehicle session. Subjects were given at least two training sessions between test sessions and were required to maintain the 80% criterion under both training conditions before each test. A range of PNU-99194A doses (1.25, 2.5, 5.0 and 10.0 mg/kg sc, 15 min) were tested, followed by stimulus generalization tests with PD 152255 (1.0, 2.0 and 3.0 mg/kg ip, 15 min) and S-14297 (1.0, 3.0 and 8.0 mg/kg sc, 30 min). Additionally, (+)-7-OH-DPAT (0.01, 0.03 and 0.1 mg/kg sc, 15 min) and haloperidol (0.5 mg/kg ip, 60 min) were administered in combination with each of four doses of PNU-99194A (1.25-10.0 mg/kg) to assess antagonism of the training stimulus.

2.6. Data analysis

The degree of stimulus generalization was 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. The mean and S.E.M. were calculated for each of these dependent measures at each dose, and the data were plotted in dose–response curves. Because some of the compounds produced a marked reduction in response rate, test results from animals that made at least 10 total responses were 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. If stimulus generalization occurred, the dose response curve was also analyzed using a nonlinear regression and ED_{50} and confidence intervals were calculated. One-way analyses of variance were conducted on response rate data. Statistical analyses were conducted using GraphPad Prism software (GraphPad, San Diego, CA).

3. Results

PNU-99194A reliably established stimulus control in all eight subjects (mean sessions to criterion=34.6±4.3; range=21–53). The PNU-99194A dose–response function in these animals was published previously (Goudie et al., 2001) and is shown again in Fig. 1. Fig. 1 also depicts the results of stimulus generalization tests with the selective DA D_3 receptor antagonists PD 152255 and S-14297. PD 152255 failed to exhibit stimulus generalization to PNU-99194A and severely disrupted responding ($F_{3,31}$=10.70, P<.001) at the doses tested. Its obvious sedative effects precluded testing of higher doses. In contrast, S-14297 exhibited partial substitution for PNU-99194A following both 3.0 and 8.0 mg/kg doses. However, only three animals completed the response requirement following the 8.0 mg/kg dose, and only one of them exhibited full generalization to PNU-99194A. Two other animals that made between 5 and 10 responses following this dose

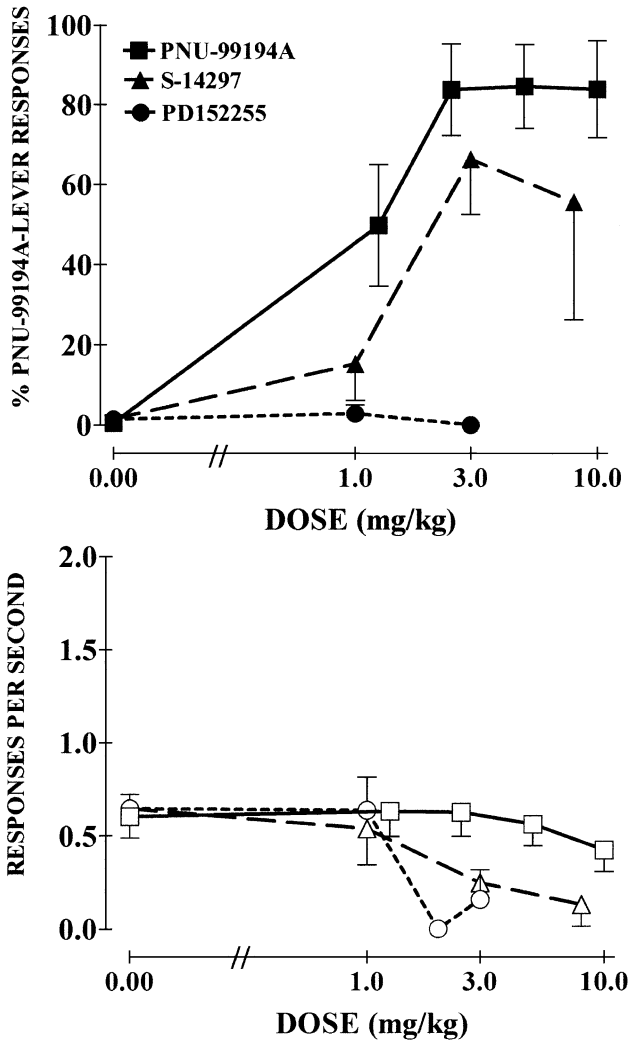

Fig. 1. Results of stimulus generalization tests with PNU-99194A, S-14297 and PD 152255. Percentage of PNU-99194A lever responses is displayed in the upper graph and response rate is displayed in the lower graph.

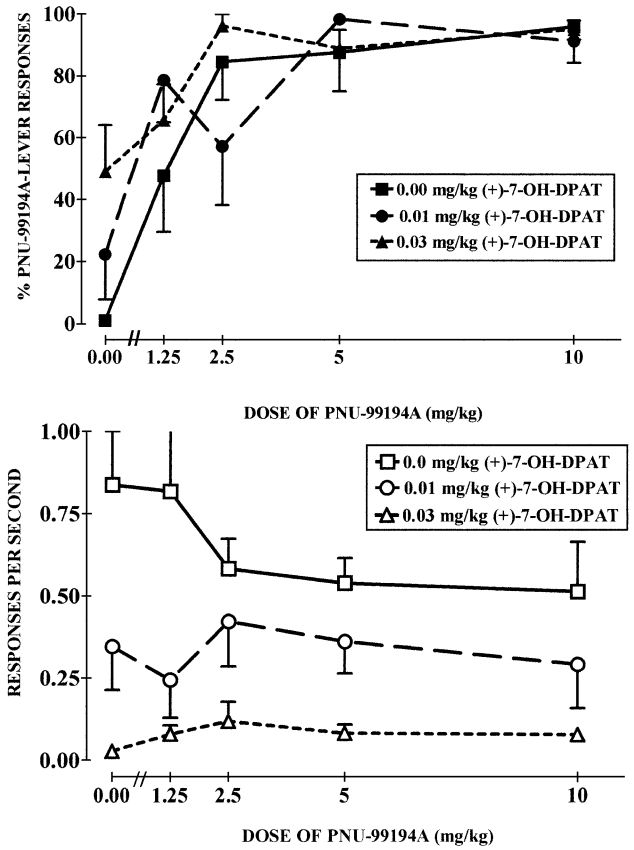

Fig. 2. Effects of (+)-7-OH-DPAT (0.01, 0.03 mg/kg) on the discrimination of PNU-99194A. Percentage of PNU- 99194A lever responses is displayed in the upper graph and response rate is displayed in the lower graph.

made the majority of their responses on the PNU-99194A lever. S-14297 produced drug-lever responding that differed significantly from saline ($F_{2,23}$=14.22, P<.001) and also significantly reduced response rate ($F_{3,23}$=4.04, P<.05). Higher doses of S-14297 were not tested due to difficulties maintaining this compound in solution at higher concentrations and at a pH that would not produce cutaneous toxicity. Unlike PD 152255, S-14297 did not appear to produce sedation at the doses tested.

Fig. 2 shows the results of tests conducted with (+)-7-OH-DPAT (0.0, 0.01 and 0.03 mg/kg) administered in combination with a range of PNU-99194A doses (0–10 mg/kg). The discrimination of PNU-99194A was not attenuated by (+)-7-OH-DPAT. In fact, this D_3-preferring agonist actually appeared to potentiate the effects of low PNU-99194A doses (1.25 and 2.50 mg/kg). Furthermore, when administered in combination with vehicle, 0.03 mg/kg (+)-7-OH-DPAT produced partial substitution (49%) for PNU-9914A. A two-way ANOVA (PNU-99194A Dose×(+)-7-OH-DPAT Dose) indicated a significant main effect of PNU-99194A dose ($F_{4,94}$=20.58, P<.0001), but the main effect of (+)-7-OH-DPAT dose was not significant. Additionally, (+)-7-OH-DPAT significantly reduced response rate ($F_{2,105}$=34.75, P<.0001). The ED_{50} of PNU-99194A was 1.25 mg/kg (95% CI: 0.38–4.16 mg/kg). When administered in combination with 0.01 mg/kg (+)-7-OH-DPAT, PNU-99194A's ED_{50} was shifted to the left (0.78 mg/kg; 95% CI: 0.10–5.77 mg/kg). However, the overlapping confidence intervals indicate that the difference between ED_{50}s was not statistically significant.

Interestingly, the D_2 antagonist haloperidol also appeared to potentiate the effects of low PNU-99194A doses and exhibited partial substitution for the training drug (see Fig. 3). Only one dose of haloperidol (0.50 mg/kg) was examined in combination with each dose of PNU-99194A. Some animals were tested following 1.0 mg/kg haloperidol in combination with PNU-99194A, but response rate was completely suppressed by this drug combination (data not shown). Full generalization (96%) occurred when 0.5 mg/kg haloperidol and 1.25 mg/kg PNU-99194A were co-administered, compared to 64% drug-appropriate responding when 1.25 mg/kg PNU-99194A was co-administered with a vehicle injection. Haloperidol (0.50 mg/kg) also produced 44% drug-appropriate responding when co-administered with vehicle. A two-factor ANOVA (Haloperidol Dose× PNU-99194A Dose) showed a significant main effect of haloperidol ($F_{1,62}$=5.12, P<.05) and a significant main effect of PNU-99194A ($F_{4,62}$=8.28, P<.0001) on percent drug-lever responses, but there was not a significant inter-

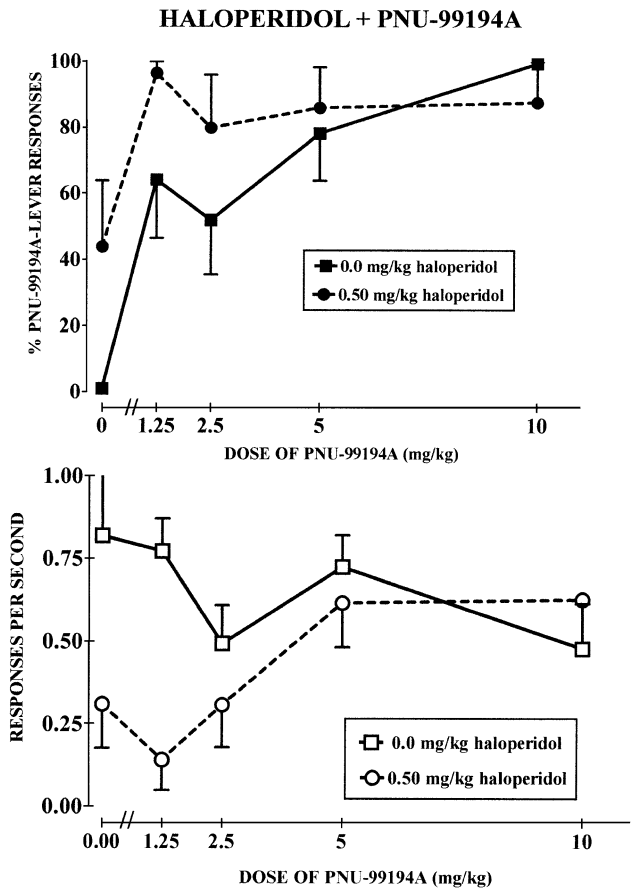

Fig. 3. Effects of haloperidol (0.50 mg/kg) on the discrimination of PNU-99194A. Percentage of PNU-99194A lever responses is displayed in the upper graph and response rate is displayed in the lower graph.

action. Again, PNU-99194A did not significantly alter response rate. Response rate was significantly reduced by haloperidol ($F_{1,70}$=9.07, P<.005).

4. Discussion

The present results confirmed previous reports that PNU-99194A establishes and maintains discriminative stimulus control in rats (Baker et al., 1997; Franklin et al., 1998; Goudie et al., 2001). Previous findings suggested the possibility that the discriminative stimulus effects of this compound are mediated primarily through DA D_3 receptor antagonism (Franklin et al., 1998). This hypothesis was based on the substitution of the PNU-99194A cue by the D_3-preferring antagonists, (−)-DS 121, (+)-AJ-76 (Franklin et al., 1998) and (+)-UH-232 (Goudie et al., 2001). In addition, initial observations that the atypical antipsychotic clozapine exhibited symmetrical stimulus generalization with PNU-99194A suggests that the stimulus properties shared by PNU-99194A and clozapine were also D_3-receptor mediated. However, this was not supported by recent findings that the more selective D_3 antagonists, PD 152255 and S-14297 failed to induce generalization to clozapine (Goudie et al., 2001). Furthermore, the present findings that PD 152255 and S-14297 also do not fully substitute for PNU-99194A question the importance of D_3 receptor mediation of the PNU-99194A cue. In fact, complete stimulus generalization to PNU-99194A by scopolamine and trihexyphenidyl (Goudie et al., 2001) indicate that antimuscarinic activity may be critically involved in the discriminative stimulus effects of PNU-99194A. However, PNU-99194A exhibited a very weak binding affinity for muscarinic receptors compared to scopolamine (Goudie et al., 2001). Therefore, the pharmacological mechanisms underlying the similarities between PNU-99194A and clozapine remain unresolved.

Although neither of the D_3 antagonists examined in the present study fully substituted for PNU-99194A, it is worth noting some apparent dissimilarities between PD 152255 and S-14297. Regarding stimulus generalization in the present study, PD 152255 produced negligible PNU-99194A-appropriate responding while S-14297 produced 66% PNU-99194A-appropriate responding. Higher doses of S-14297 may have produced full generalization, but difficulty in maintaining this compound in solution without lowering the pH to levels that would cause cutaneous toxicity precluded administration of higher doses in the present study. Further, although both PD 152255 and S-14297 suppressed response rates relative to PNU-99194A, PD 152255 engendered greater rate-suppressant effects than PNU-99194A and S-14297. Moderate PD 152255 doses (2.0–3.0 mg/kg) were noted to produce marked sedation. Although S-14297 also significantly reduced response rates, this compound did not appear to produce sedative effects. It is important to note that response rate disruption in a drug discrimination assay may not be directly related to drug effects on general locomotor activity and only casual behavioral observations suggest that the effects of PD 152255 on activity were distinctly different from those following either S-14297 or PNU-99194A administration. More relevant behavioral assays designed to assess locomotor activity have documented that PD 152255 significantly reduced spontaneous locomotor activity in rats following intraperitoneal injection of doses comparable to those examined in the present study (Corbin et al., 1998). However, in rats acclimated to the testing environment prior to subcutaneous drug administration, PD 152255 (1.0–10.0 mg/kg) increased locomotor activity (Corbin et al., 1998). Similar effects have been noted with other D_3 antagonists including PNU-99194A (Waters et al., 1993) and nafadotride (Sautel et al., 1995).

In a recent study by Millan et al. (2000), S-14297, along with several other D_3 receptor antagonists, were investigated for blockade of 7-OH-DPAT or PD 128907 discrimination. The more selective D_3 antagonists (S-14297, S11566 and GR 218,231) did not block the discrimination of either PD 128907 or 7-OH-DPAT, while less selective compounds blocked the discrimination of 0.16 mg/kg PD 128907 (AJ76, UH-232 and nafadotride) or 0.16 mg/kg 7-OH-DPAT (nafadotride and PNU-99194A). This is contrary to other recent reports that PNU-99194A does not block the discrimination of 7-OH-DPAT (Depoortere et al., 2000) or (+)-7-OH-DPAT (Baker et al., 1999; Christian et al., 2001). Depoortere et al. (2000) used a slightly lower training dose of 7-OH-DPAT (0.10 mg/kg), but examined a comparable dose range of PNU-99194A (1.0–10.0 mg/kg) to that tested in the Millan et al.'s (2000) study. In our preliminary studies, the discrimination of 0.03 mg/kg (+)-7-OH-DPAT was also not blocked by PNU-99194A (5.0–20.0 mg/kg); a dose of 40.0 mg/kg PNU-99194A partially attenuated the training drug cue, but disrupted responding in most subjects (Baker et al., 1999). A more thorough investigation of PNU-99194A effects on a range of (+)-7-OH-DPAT doses confirmed our preliminary findings that the discriminative stimulus effects of (+)-7-OH-DPAT are not blocked by PNU-99194A (Christian et al., 2001).

Depoortere et al. (2000) also examined a single dose of PNU-99194A (10 mg/kg) in combination with a range of 7-OH-DPAT doses (0.003–0.10 mg/kg) and demonstrated a leftward shift in the 7-OH-DPAT dose response function. The present results complement those findings, given that potentiation of PNU-99194A appropriate-responding was observed when doses of (+)-7-OH-DPAT (0.01 and 0.03 mg/kg) were tested in combination with each of four PNU-99194A doses (1.25–10.0 mg/kg). Thus, it appears that (+)-7-OH-PAT improved discrimination of lower PNU-99194A doses and, in fact, (+)-7-OH-DPAT (0.03 mg/kg) actually produced partial substitution for PNU-99194A in the present study. Whether the synergistic actions between PNU-99194A and (+)-7-OH-DPAT are D_3- or D_2-mediated therefore remains undetermined.

Depoortere et al. (2000) offered the tentative explanation that PNU-99194A may act as a partial DA agonist. This explanation is supported to some degree by in vitro data that PNU-99194A may possess some intrinsic activity at D_3 receptors (Haadsma-Svensson and Svensson, 1998). Recent investigations of in vitro functional activity by Perachon et al. (2000) have also described S-14297 as a full D_3 agonist and partial D_2 agonist. These findings offer an alternative explanation that S-14297 partial substitution for PNU-99194A is mediated by D_3 and/or D_2 agonism. The observation that potentiation and partial substitution also occurred with haloperidol may also be explained by PNU-99194A's partial agonist properties given previous reports that D_2 and D_3 receptors function in opposing manners (Svensson et al., 1994; Diaz et al., 1994). Moreover, reversal of haloperidol-induced rate suppression by PNU-99194A (see Fig. 3) in the present study supports the possible involvement of D_2 receptor agonist activity.

In summary, the current study supplements our recent report (Goudie et al., 2001) that the discriminative stimulus properties of PNU-99194A are mediated by a more complex pharmacological profile than originally conceived. Once thought to be a highly selective D_3 receptor antagonist and a potential tool to investigate the functional significance of this receptor subtype, PNU-99194A appears to involve a complex combination of D_3 receptor antagonism, D_2 and/or D_3 partial agonism (present results), and muscarinic antagonism (Goudie et al., 2001). Since the current study was conducted, several more potent and selective D_3 receptor ligands have been synthesized, including NGB 2904 and NGB 2849 which boast 150–290-fold greater affinities for D_3 than D_2, respectively (Yuan et al., 1998). The use of such highly selective ligands may be useful for further in vivo characterization of the D_3 DA receptor.

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