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# 7-OH-DPAT Has *d*-Amphetamine-like Discriminative Stimulus Properties

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BEVINS, R. A., J. E. KLEBAUR AND M. T. BARDO. *7-OH-DPAT has d-amphetaminelike discriminative stimulus properties*. PHARMACOL BIOCHEM BEHAV **58**(2) 485–490, 1997.—Rats were trained on a *d*-amphetamine (1 mg/kg) vs. saline discrimination task using food-maintained responding (fixed ratio = 25). In extinction tests, drug-appropriate responding decreased as the dose of amphetamine was substituted for the training dose decreased. The dopamine D2/D3 receptor agonist (±)7-hydroxy-*N*,*N*-di-*n*-propyl-2-aminotetralin (7-OH-DPAT) substituted fully for the amphetamine discriminative stimulus at the higher doses examined (0.1, 0.3, 1.0 mg/kg). This substitution was accompanied by a substantial decrease in overall response rates. Eticlopride, a dopamine D2/D3 receptor antagonist, partially blocked 7-OH-DPAT substitution. Thus, at the higher doses, 7-OH-DPAT shared sufficient discriminative stimulus properties with the amphetamine to prompt full substitution. Eticlopride antagonism suggests a role for the D2/D3 dopamine receptor in this substitution. © 1997 Elsevier Science Inc.

Amphetamine Dopamine D2 and D3 receptors Drug discrimination Eticlopride Operant conditioning

THERE has been a recent flurry of work examining the behavioral effects of the dopamine D2/D3 agonist 7-hydroxy-*N*,*N*-di-*n*-propyl-2-aminotetralin [7-OH-DPAT (2,3,10,12,14, 21,22)]. Although investigators are still debating whether 7-OH-DPAT-induced effects result primarily from D3 receptor activation or from both D2 and D3 receptor activation (5,15, 16,25,29,30), it is clear that 7-OH-DPAT is effective in behavioral paradigms often used to assess the abuse potential of drugs [e.g., self-administration, place conditioning and drug discrimination (9,20,28,34)].

This effectiveness of 7-OH-DPAT has been demonstrated in the self-administration paradigm. For instance, cocaine self-administration in rats is attenuated when 7-OH-DPAT is combined with cocaine (6,7). One possible explanation for the reduction in cocaine self-administration is that 7-OH-DPAT is reinforcing itself. Consistent with this notion, 7-OH-DPAT alone maintains self administration [16–128 μg/infusion (6)], produces a conditioned place preference [5 mg/kg (26)] and potentiates *d*-amphetamine enhancement of intracranial self-stimulation [24 nmol/kg (23)]. These and related results have prompted investigators to suggest that 7-OH-DPAT (or other putative D3-preferring agonists) may be useful in the treatment of drug dependence (1,6,7,10).

In the drug discrimination preparation, 7-OH-DPAT can serve as a discriminative stimulus in rats (27), and these discriminative stimulus properties are similar to cocaine (1). That is, 7-OH-DPAT will control cocaine-appropriate responding. However, because 7-OH-DPAT has not been shown to be substituted for stimulant drugs other than cocaine, it is not clear whether 7-OH-DPAT has discriminative stimulus properties similar to cocaine only or psychostimulant drugs more generally. Moreover, it is not known if the stimulant-like discriminative stimulus effect of 7-OH-DPAT depends on stimulation of D2/D3 receptors. Thus, the present experiment examined the ability of (±)7-OH-DPAT to occasion responding controlled by a *d*-amphetamine discriminative stimulus and sought to determine if a D2/D3 antagonist would alter this response.

## MATERIALS AND METHODS

### *Animals*

The subjects were 15 male Sprague-Dawley rats obtained from Harlan Industries (Indianapolis, IN). Each rat was housed individually in a hanging stainless steel cage in a colony room on a 12-h light–dark cycle. Water was available con-

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tinuously in the home cage. Food access was restricted such that each rat was maintained at approximately 80% of its free-feeding weight. Before the start of the present experiment, all rats were in a separate experiment in which they experienced 10 exposures to boxes different from the operant chambers. On the 10th exposure, each rat received a single intraperitoneal injection of 1 mg/kg *d*-amphetamine. One box was a three-compartment chamber with two end compartments (29 × 23 × 45 cm) and a smaller center gray compartment (19 × 23 × 45 cm). One end compartment had white walls, mesh floor and pine bedding; the other end had black walls, rod floor and cedar bedding. The other box was a black chamber (31.5 × 29 × 46 cm) with a mesh floor and a black cloth liner for bedding.

*Apparatus*

Six Med Associate operant boxes (ENV-001, St. Albans, VT) were housed in sound-attenuating chambers. Each box, with the inside dimensions of 28 × 21 × 20.9 cm (l × w × h), was made of a rod floor, stainless-steel end walls and clear Plexiglas side walls and ceiling. The floor was composed of 18 rods, 5 mm in diameter, spaced 1.6 cm apart center to center. Situated in the bottom center of the front panel was a 5- × 4.2-cm (l × h) opening to a recessed food tray. Mounted on each side of the food tray was a metal response bar. The center of each bar was mounted 7.3 cm from the grid floor and 4.2 cm from its respective Plexiglas side wall. A 28-V cue light, 3 cm in diameter, was centered about 6 cm above each bar. A 486DX2 personal computer with Med Associate interfacing controlled the experimental sessions and collected the data. Bar-pressing was maintained by 45-mg sucrose pellets (P. J. Noyes Co., Lancaster, NH).

*Drugs*

The *d*-amphetamine sulfate (Sigma, St. Louis, MO), (±)7-OH-DPAT, and S(−)-eticlopride hydrochloride (both purchased from Research Biochemicals International, Natick, MA) were dissolved in saline (0.9% NaCl). Amphetamine and eticlopride were injected intraperitoneal (IP), and 7-OH-DPAT was injected either IP or subcutaneously (SC). All dosages were calculated based on the salt form of the drugs.

*Procedure*

*Preliminary training.* On day 1, rats were magazine trained. Both bars were mounted in the box, and each spontaneous response resulted in delivery of a sucrose pellet. On day 2, only the left bar was mounted in the box, and rats were shaped to press the bar. Which response bar (left or right) was mounted in the box alternated daily. Across the daily sessions, the fixed ratio (FR) response requirement (number of consecutive bar presses needed to receive a pellet) was gradually increased from FR 1 to FR 25. The start of each session was signaled by the onset of the cue lights mounted above the bars; offset of these lights signaled the end of the session. The function of these lights remained constant throughout all phases of the present experiment. Except where noted, all sessions were 15 min. Preliminary training was considered complete when the rat was on an FR 25 schedule, and it earned 20 reinforcers in two separate sessions.

*Amphetamine discrimination.* The procedures for amphetamine discrimination training and substitution testing were adapted from previously published work in the drug-discrimination field (13,19). Discrimination training was conducted Monday through Friday. For the remaining phases of the experiment, both bars were mounted in the box. Amphetamine (1 mg/kg) or saline was injected IP 15 min prior to the start of the session [cf. (18)]. The left bar was the amphetamine-correct bar for eight rats. The remaining seven rats had the right bar as the amphetamine-correct bar. This bar-alternating procedure was also applied to each operant box. For eight rats, the injection sequence for daily sessions was 2 amphetamine days followed by 2 saline days. This pattern was repeated throughout the experiment. For the remaining seven rats, the sequence was reversed. On Monday, Wednesday and Friday, injection-appropriate responding was reinforced on an FR 25 schedule of reinforcement for the entire 15-min session. The 25th response on the appropriate bar produced a pellet regardless of the number of bar presses that occurred on the inappropriate bar. To assess the control of injected solution over responding, extinction tests were given every Tuesday and Thursday (i.e., one saline and one amphetamine test per week). The extinction test was conducted in the first 2 min of the 15-min session. In the 2-min extinction period, the distribution of responding was monitored, but bar pressing did not result in pellet delivery. In the remaining 13 min of the session, the computer program reverted back to providing contingent reinforcement for injection-appropriate responding. Acquisition criteria for the amphetamine/saline discrimination were satisfied by (a) completion of the first FR 25 on the correct bar for 10 consecutive sessions and (b) four consecutive extinction periods with 80% or better responding on the injection-appropriate bar. Rats were shifted to the amphetamine-substitution phase after satisfying these criteria.

*Amphetamine substitution.* The amphetamine-substitution phase was similar to the discrimination phase except that the Friday session was changed to a 4-min extinction test (no reinforced responding). In that test, rats ($n = 15$) were injected IP with 0.0625, 0.125, 0.25, 0.5, 1.0 or 2.0 mg/kg amphetamine. The test dose was injected 15 min before the start of the session. Each amphetamine dose was administered twice according to a randomized block design. Friday testing was conducted only if the rat responded at 80% or better in the Tuesday and Thursday 2-min extinction periods. This criterion was in force throughout the remainder of the experiment. Rats that did not satisfy this criterion were left in the home cage on Friday and given their daily food maintenance.

*7-OH-DPAT substitution.* Immediately following the amphetamine-substitution phase, we assessed the ability of 7-OH-DPAT to cause amphetamine-appropriate responding. The procedure was identical to the amphetamine substitution except that 7-OH-DPAT rather than amphetamine was injected 15-min prior to the Friday test. Ten rats received the following doses of 7-OH-DPAT in a mixed order: 0.0, 0.01, 0.03, 0.1, 0.3 and 1.0 mg/kg. Half of the rats received the 7-OH-DPAT injected IP, and the other half received 7-OH-DPAT injected SC. For each rat, the route of administration was switched after it had been tested with each dose. Using SC injections of 7-OH-DPAT on the test days allowed us to make comparisons with previous work showing the substitution of 7-OH-DPAT for cocaine (1). However, we were concerned that rats could use the injection route (SC vs. IP) as a stimulus for change in drug. That is, amphetamine and saline were always injected IP on the discrimination training days; a SC injection could be very distinct to these rats given their chronic experience with IP injections. Thus, employing the same 7-OH-DPAT substitution protocol with IP injections allowed us to assess this possibility.

*Eticlopride antagonism.* The ability of eticlopride, a dopamine D2/D3 receptor antagonist, to block the substitution of 7-OH-DPAT for amphetamine was also assessed. Rats re-

ceived pretreatment with eticlopride (IP, 0.01 or 0.05 mg/kg) 30–45 min before the Friday substitution test. Fifteen minutes before extinction testing, rats were injected SC with one of the following doses of 7-OH-DPAT in a mixed order: 0.0, 0.03, 0.1 or 0.3 mg/kg. Because 7-OH-DPAT injected SC substituted for amphetamine at a lower dose than IP (see Results), we choose the SC route to optimize our chance of surmounting any eticlopride blockade that could occur. Across the 7-OH-DPAT doses, three rats were tested with both doses of eticlopride, four other rats were tested with only the 0.01 mg/kg eticlopride dose, and an additional four rats were tested only at the 0.05 mg/kg eticlopride dose. If eticlopride failed to block 7-OH-DPAT substitution, it would implicate receptors other than the D2/D3 receptors in the shared discriminative stimulus effects between amphetamine and 7-OH-DPAT [for dopamine binding specificity of eticlopride, see (4,17,24)]. Indeed, 7-OH-DPAT also binds to sigma receptors (33).

*Data Analyses*

Because 7-OH-DPAT has rate-suppressant effects, we had to adopt criteria for exclusion of data from rats for the analyses and figures. If a rat made fewer than 10 responses in the 4-min Friday extinction test after the completion of the experiment, the data were not included in either the statistical analyses or in the figures of the current report. Several rats at the higher doses of 7-OH-DPAT (or 7-OH-DPAT and eticlopride) failed to meet the 10-response criterion for inclusion in data analyses. This failure left a cell or two of the design empty for many of the rats and in turn produced a substantial loss of data during analysis (i.e., all data for a rat were deleted from a repeated measure analysis of variance if there was a missing data point). Thus, to use all available data, we employed Student's *t*-tests for all comparisons, using a two-tailed rejection region. To control for family-wise error associated with multiple *t*-tests, we declared alpha as 0.05 (traditional value) divided by the number of comparisons. For example, alpha for the comparison between the training dose of amphetamine to 7-OH-DPAT doses injected SC (six different doses) was equal to 0.05/6 or 0.0083.

The percentage of amphetamine-appropriate responding was calculated with the following formula: total number of responses on amphetamine bar in the 4-min extinction session divided by the total number of responses on both bars in that session $\times 100$. Complete substitution for the amphetamine-discriminative stimulus was declared if the percentage of drug-appropriate responding was statistically similar to the percentage of drug-appropriate responding engendered by the 1 mg/kg training dose of amphetamine. A similar procedure was used for response suppression. Partial substitution was defined as amphetamine-appropriate responding above the saline criterion but not to the level controlled by the amphetamine training dose.

## RESULTS

*Preliminary Training and Amphetamine Discrimination*

The average number of sessions for rats to reach the FR 25 schedule of reinforcement was 13.1 ± 0.7 SEM. All rats acquired the amphetamine/saline discrimination. The average number of trials to meet the discrimination criteria was 39.2 ± 5.6 SEM.

*Amphetamine and 7-OH-DPAT Substitution*

Figure 1A shows the results from the amphetamine- (left half) and 7-OH-DPAT- (right half) substitution phases. For the amphetamine-substitution graph, each mean and SEM represents the average of the two tests for each dose of amphetamine. During the amphetamine-substitution tests, the percentage of drug-appropriate responses at the 1 mg/kg amphetamine training dose was well above the 80% discrimination criterion. This value was used throughout the report to determine statistically whether full substitution to the discriminative stimulus effects of amphetamine was obtained. In the amphetamine-substitution phase, the 0.5 and 2 mg/kg doses of amphetamine substituted fully for the training dose. In contrast to the amphetamine training dose, statistically less drug-correct responding was occasioned by the 0.0625 [$t(28) = 26.86$, $p < 0.001$], 0.125 [$t(28) = 19.29$, $p < 0.001$] and 0.25 [$t(28) = 7.47$, $p < 0.001$] mg/kg doses of amphetamine. The median effective dose ($ED_{50}$) for amphetamine, based on the linear portion of the substitution curve, was 0.26 mg/kg.

The right panel of Fig. 1A shows the mean percentage of amphetamine-appropriate responding in the 7-OH-DPAT-substitution phase. Regardless of injection route, 7-OH-DPAT fully substituted for the amphetamine discriminative stimulus at the higher doses assessed. When 7-OH-DPAT was injected SC, it appeared to substitute fully for amphetamine at a lower

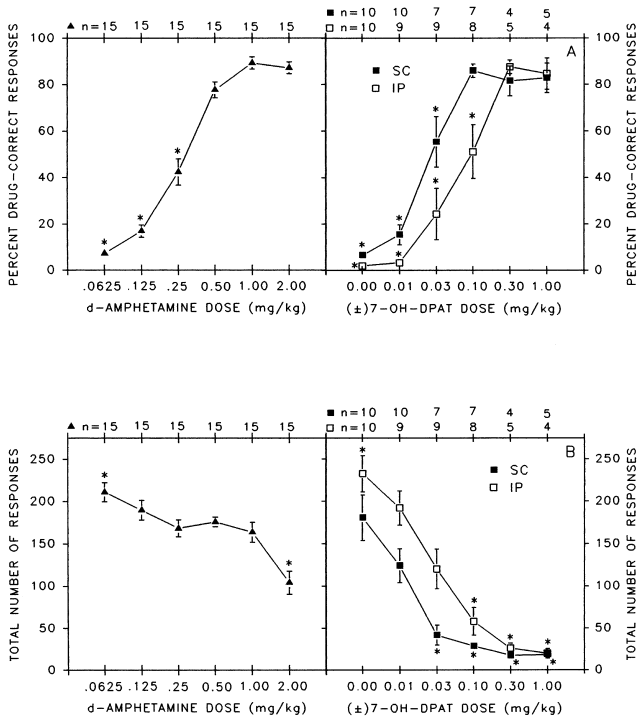


FIG. 1. A shows the mean percentage of amphetamine-appropriate responding (±1 SEM) from the amphetamine (left) and the 7-OH-DPAT (right) substitution phases. B shows the total number of responses (±1 SEM) in the 4-min extinction sessions from the amphetamine (left) and the 7-OH-DPAT (right) substitution phases. Solid squares represent rats that had subcutaneous (SC) injections of 7-OH-DPAT; open squares represent rats that had intraperitoneal (IP) injections of 7-OH-DPAT. The number of rats that met the criterion for inclusion in the analyses and graphs at each amphetamine and 7-OH-DPAT dose is denoted across the top of the graph. *Significant difference from the training dose of amphetamine (1 mg/kg).

dose (0.1 mg/kg) than when it was injected IP (0.3 mg/kg). Statistical analyses confirmed this impression. Amphetamine-appropriate responding at the 0.1 mg/kg 7-OH-DPAT dose was significantly below the amphetamine training dose when injected IP [$t(21) = 4.23$, $p < 0.001$] but not when injected SC ($t < 1$). Relative to the amphetamine training dose, 7-OH-DPAT injected IP also controlled significantly less amphetamine-appropriate responding at the 0.0 [$t(23) = 27.10$, $p < 0.001$], 0.01 [$t(22) = 24.77$, $p < 0.001$] and 0.03 [$t(21) = 7.47$, $p < .001$] mg/kg doses. Similarly, 7-OH-DPAT injected SC controlled significantly less drug-appropriate responding than the amphetamine training dose at the 0.0 [$t(23) = 23.26$, $p < 0.001$], 0.01 [$t(23) = 15.63$, $p < 0.001$] and 0.03 [$t(20) = 4.17$, $p < 0.001$] mg/kg doses. Using a conservative control for family-wise error ($\alpha = 0.0083$ for the present comparisons), the percentage of amphetamine-correct responding did not differ significantly between injection routes at any dose of 7-OH-DPAT tested; the 0.1 mg/kg dose had the largest $t$-value [$t(13) = 2.75$, $p = 0.017$], and the 1.0 mg/kg dose had the smallest $t$-value ($t < 1$). The $ED_{50}$ for 7-OH-DPAT injected SC was 0.04 mg/kg, whereas the $ED_{50}$ for the IP condition was 0.11 mg/kg.

The left half of Fig. 1B shows the total number of responses on both bars during the entire 4-min extinction tests for the amphetamine-substitution phase. The amphetamine values represent the average of the two tests for each dose of amphetamine. Relative to the amphetamine training dose, there was significantly more responding at the 0.0625 mg/kg dose of amphetamine [$t(28) = 2.90$, $p = 0.007$] and significantly less responding at the 2.0 mg/kg dose [$t(28) = 3.30$, $p = 0.003$].

The right half of Fig. 1B shows the mean number of responses in the 4-min extinction periods for each dose of 7-OH-DPAT injected either SC or IP. Dose-dependent decreases in responding were observed. This response disruption occurred at a lower dose when 7-OH-DPAT was injected SC (0.03 mg/kg). When 7-OH-DPAT was injected SC, it significantly reduced overall responding relative to the amphetamine training dose at the 0.03 [$t(20) = 6.34$, $p < 0.001$], 0.1 [$t(20) = 7.65$, $p < 0.001$], 0.3 [$t(17) = 6.27$, $p < 0.001$] and 1.0 [$t(18) = 6.96$, $p < 0.001$] mg/kg doses. When 7-OH-DPAT was injected IP, there was significantly less responding at the 0.1 [$t(21) = 5.24$, $p < 0.001$], 0.3 [$t(18) = 6.53$, $p < 0.001$] and 1.0 [$t(17) = 6.13$, $p < 0.001$] mg/kg doses, compared with response levels at the amphetamine training dose. Lastly, there was significantly more responding by rats given an IP injection of saline (0.0 mg/kg 7-OH-DPAT) than occurred with the training dose of amphetamine [$t(23) = 3.04$, $p = 0.006$]. This result replicates the difference seen in the amphetamine-substitution phase. Interestingly, overall responding when saline was injected SC was comparable to the responding under the 1 mg/kg amphetamine and not saline. The difference in responding when saline was injected IP vs. SC suggests that the rats were able to discriminate between injection routes. However, the overall levels of bar pressing did not differ significantly between injection routes at any 7-OH-DPAT dose assessed ($\alpha = 0.0083$ for present comparisons); the 0.03 mg/kg dose had the largest $t$-value $t(14) = 2.73$, $p = 0.016$ and the 1.0 mg/kg dose had the smallest $t$-value ($t < 1$).

### *Eticlopride Antagonism*

Because rats pretreated with 0.01 and 0.05 mg/kg eticlopride did not differ statistically in the percentage of responding on the drug bar at any dose of 7-OH-DPAT tested, the data were combined for graphic display and subsequent analyses. Figure 2A shows the mean percentage of responding on the amphetamine bar for those rats pretreated with eticlopride (0.01 and 0.05 mg/kg pooled). For comparison, the cor-

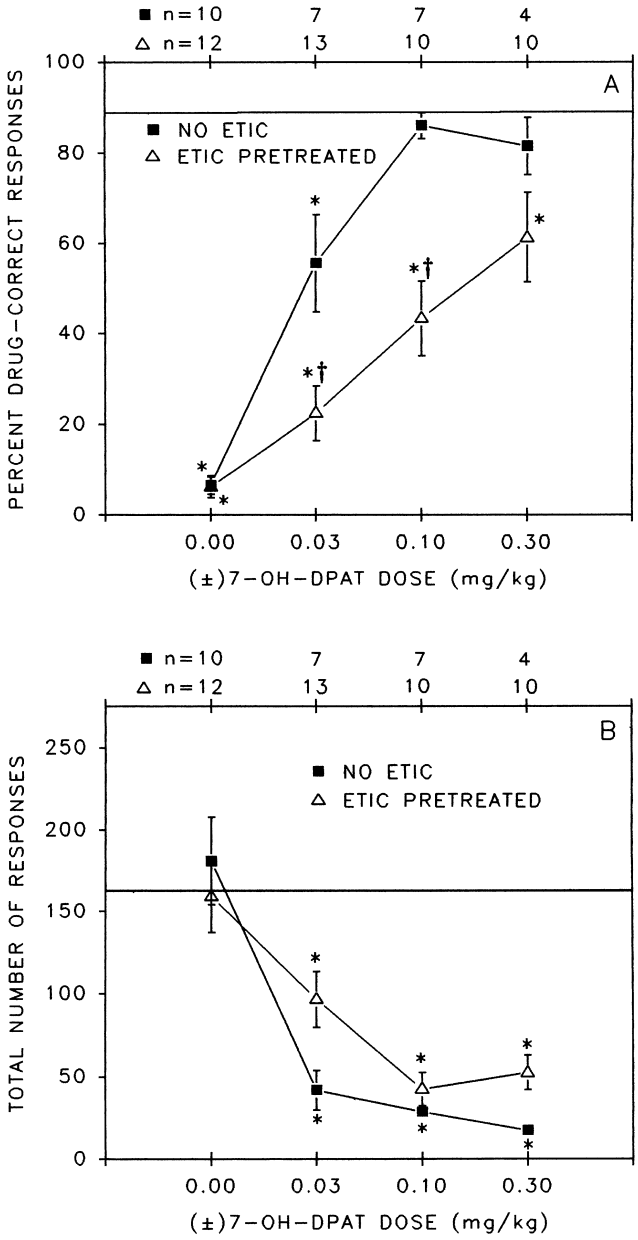


FIG. 2. A shows the mean percentage of amphetamine-appropriate responding (±1 SEM), and B shows the mean number of responses (±1 SEM) from the eticlopride antagonism phase. Solid squares represent rats that had SC injections of 7-OH-DPAT without eticlopride pretreatment. Open triangles represent the pooled data from rats pretreated with eticlopride (0.01 and 0.05 mg/kg). The horizontal line through each panel denotes the value for the training dose of amphetamine. The number of rats that met the criterion for inclusion in the analyses and graphing at each 7-OH-DPAT dose is denoted across the top of the graph. *Significant difference from the training dose of amphetamine (1 mg/kg). †Significant difference between eticlopride pretreated and nonpretreated rats.

responding 7-OH-DPAT data from the previous phase in which rats were not pretreated with eticlopride (SC injection only) is also plotted. The solid horizontal line within the graph denotes the mean level of drug-appropriate responding controlled by the amphetamine training dose. Pretreatment with eticlopride prevented the full substitution of 7-OH-DPAT to the amphetamine discriminative stimulus. The difference between eticlopride pretreatment and the amphetamine training dose was significant at the 0.0 [$t(25) = 22.92$, $p < 0.001$], 0.03 [$t(26) = 10.70$, $p < 0.001$], 0.1 [$t(23) = 6.18$, $p < .001$] and 0.3 [$t(23) = 3.22$, $p = 0.004$] mg/kg doses of 7-OH-DPAT. The percentage of drug-appropriate responding between the eticlopride pretreated and nonpretreated condition differed significantly at the 0.03 [$t(18) = 2.90$, $p = 0.01$] and 0.1 [$t(15) = 4.14$, $p < 0.001$] mg/kg doses of 7-OH-DPAT.

Figure 2B shows the total number of responses for rats pretreated with eticlopride. Because the eticlopride conditions (0.01 and 0.05 mg/kg) did not differ statistically, they were pooled. For comparison, Fig. 2B includes the corresponding 7-OH-DPAT data from the previous phase in which rats were not pretreated with eticlopride (SC injection only). Overall responding for the eticlopride pretreated group was significantly lower than that obtained with the training dose of amphetamine at the 0.03 [$t(28) = 3.23$, $p = 0.003$], 0.1 [$t(23) = 7.27$, $p < 0.001$] and 0.3 [$t(23) = 6.60$, $p < 0.001$] mg/kg doses. Eticlopride appeared to prevent some of the response suppression induced by 7-OH-DPAT. However, using a conservative control for family-wise error ($\alpha = 0.0125$ for the present comparisons), the overall levels of bar pressing did not differ between the eticlopride pretreated and nonpretreated conditions at any dose of 7-OH-DPAT; the 0.03 mg/kg dose had the largest $t$-value [$t(18) = 2.19$, $p = 0.042$] and the 0.0 mg/kg dose had the smallest $t$-value ($t < 1$).

## DISCUSSION

In the present report, we found that 1.0 mg/kg amphetamine served as a discriminative stimulus for food-maintained responding and that substitution to this discriminative stimulus differed as a function of amphetamine dose. Regardless of injection route (IP or SC), 7-OH-DPAT completely substituted for the amphetamine discriminative stimulus in a dose-dependent manner. Also, increasing doses of 7-OH-DPAT produced profound response suppression. Eticlopride, a D2/D3 receptor antagonist, blocked the complete substitution of 7-OH-DPAT for the amphetamine discriminative stimulus.

Substitution for the amphetamine discriminative stimulus by 7-OH-DPAT tended to be associated with response suppression. However, two pieces of data argue strongly against any suggestion that response suppression rather than drug state controlled the distribution of bar pressing (i.e., percentage of drug-correct responding). First, doses of amphetamine that engendered similar response rates (0.125, 0.25, 0.5, 1.0 mg/kg) yielded a differential distribution of drug-appropriate responding. Second, doses of 7-OH-DPAT that induced response rates comparable to the 1 mg/kg training dose of amphetamine did not fully substitute for amphetamine.

Related drug discrimination work has found full substitution by (±)7-OH-DPAT for a cocaine discriminative stimulus (1). The doses of (±)7-OH-DPAT that prompted the full degree of amphetamine-appropriate responding in the present study (0.1, 0.3, 1.0 mg/kg; SC) were similar to the doses that also fully substituted for cocaine (0.3 and 1.0 mg/kg, SC). Other researchers have suggested that the neural processes mediating the discriminative stimulus effect of cocaine and amphetamine partly overlap [e.g., (8,11)]. The substitution of 7-OH-DPAT for amphetamine found in the present work is consistent with this notion. Moreover, the suggested clinical applications for 7-OH-DPAT (or other putative D3-preferring agonists) in the treatment of cocaine dependence (1,6,7) may also apply to amphetamine dependence.

When injected SC, 7-OH-DPAT substituted fully for amphetamine at a lower dose than when it was injected IP. This result may reflect a difference in the pharmacokinetics of 7-OH-DPAT injected SC vs. IP (e.g., absorption rate, first pass through liver). Related to this result is the finding that animals were sensitive to injection route. Unlike rats injected SC, rats that received an IP injection of saline responded more in the extinction tests. Moreover, a higher dose of 7-OH-DPAT was required to suppress responding below the amphetamine training dose level when 7-OH-DPAT was injected IP. At least for overall responding, the ability to discriminate between injection routes rather than between pharmacokinetic differences may account for the 7-OH-DPAT-induced response suppression difference seen with SC vs. IP injections.

In general, 7-OH-DPAT had a pronounced suppressant effect on bar pressing. By using different training and testing procedures from the present study, other researchers have also reported severe bar-press disruption by 7-OH-DPAT (1,14). Although there was a trend toward eticlopride pretreatment partly blocking this disruption at a low dose of 7-OH-DPAT (0.03 mg/kg), it was not significant. A previous report, however, has shown that disruption of variable-interval responding induced by 7-OH-DPAT was blocked by the D2/D3 antagonist sulpiride (14).

There is mixed evidence for the involvement of the dopamine D2 and/or D3 receptors in the discriminative stimulus effects of amphetamine. Smith et al. (31) found that the D2/D3 agonist quinpirole fully substituted for an amphetamine discriminative stimulus. However, Van Groll and Appel (32) found only partial substitution of quinpirole for amphetamine, and they failed to block the discriminative stimulus effects of amphetamine with the putative D2 antagonist metoclopramide. In the present study, the D2/D3 antagonist eticlopride partly blocked substitution of 7-OH-DPAT for amphetamine in the dose range examined. We attempted to use higher doses of eticlopride (0.15 and 0.50 mg/kg; data not shown) to more fully block substitution. However, these doses of eticlopride, in combination with the doses of 7-OH-DPAT that fully substituted for amphetamine, produced complete response suppression in most of the rats assessed. Thus, based on the low-dose eticlopride data, 7-OH-DPAT substitution for the amphetamine discriminative stimulus apparently involves, at least in part, activation of dopamine D2/D3 receptors. However, because neither 7-OH-DPAT nor eticlopride is completely selective for D2 or D3 receptors, the present results do not identify which of these two dopamine receptor subtypes is specifically involved in the substitution for amphetamine.

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