Biphasic effects of 7-OH-DPAT on the acquisition of responding for conditioned reward in rats

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Abstract

Previous studies have shown that dopamine (DA) receptor subtype-specific agonists differentially affect responding for conditioned reward D1-like agonists impair, whereas D2-like agonists enhance responding. The present study compared the effects of the D2-like agonists bromocriptine and 7-hydroxy-N,N-di-n-propyl-2-aminotetralin (7-OH-DPAT). Food-deprived rats ($N = 159$) were preexposed to a chamber with two levers, one producing a tone (3 s) and the other turning the house lights off (3 s), for five 40-min sessions. In four subsequent 65-min conditioning sessions with the levers removed, the lights-off stimulus was paired with food (80 presentations per session). During two 40-min test sessions, the lights-off (CR) and tone (NCR) levers were replaced and responses at each lever were recorded. Confirming previous results, bromocriptine (0.50–5.0 mg/kg) dose-dependently enhanced responding on the lever producing conditioned reward. In contrast, 7-OH-DPAT had a biphasic effect on responding for conditioned reward. Low doses (0.10–0.25 mg/kg) reduced CR lever responding, whereas a higher dose of 1.0 mg/kg enhanced such responding. An intermediate dose of 0.50 mg/kg neither impaired nor enhanced CR lever responding. The biphasic profile of 7-OH-DPAT may arise through differential actions at D3 vs. D2 receptors or presynaptic vs. postsynaptic DA receptors at low and high doses, respectively. © 2001 Elsevier Science Inc. All rights reserved.

1. Introduction

Neutral stimuli can come to acquire rewarding properties following repeated pairing with intrinsically rewarding stimuli. These previously neutral stimuli then have the ability to act as rewards themselves and are thus referred to as conditioned rewards. There is abundant evidence suggesting that dopaminergic neurotransmission plays a key role in the acquisition of responding for conditioned reward (see Sutton and Beninger, 1999 for review). Thus, systemic administration of the indirect dopamine (DA) agonists pipradol and amphetamine enhances responding on a lever producing conditioned reward (Mazurski and Beninger, 1986; Robbins, 1978; Robbins et al., 1983), whereas the DA antagonist α-flupenthixol blocks such responding (Fletcher and Higgins, 1997; Killcross et al., 1997; Robbins et al., 1983).

In contrast to the effects of indirect DA agonists, the direct DA agonist apomorphine impairs responding for conditioned reward (Beninger and Ranaldi, 1992; Robbins et al., 1983). It has been suggested that apomorphine, by directly stimulating postsynaptic DA receptors, masks a DA signal associated with reward. The indirect agonists pipradol and amphetamine, on the other hand, stimulate the release of endogenous DA without directly stimulating postsynaptic receptors; thus, the DA reward signal is left intact and is augmented by enhanced DA release (Beninger and Ranaldi, 1992; Robbins et al., 1983).

Other evidence suggests that apomorphine produces its "masking" effects by stimulating a specific DA receptor subtype. DA can bind to any of at least five distinct receptors, that are commonly dichotomized into D1-like (D1, D5) and D2-like (D2, D3, D4) receptors, depending on whether binding leads to stimulation or inhibition, respectively, of adenylate cyclase activity (Civelli et al., 1993; Niznik and Van Tol, 1992; Sibley et al., 1993). Systemic administration of D1-like agonists reliably disrupts the acquisition of responding for conditioned reward. A disruption has been reported for the partial D1-like

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agonists SKF 38393, SKF 81297, SKF 77434, and CY 208–243, as well as the full D1-like agonist SKF 82958 (Beninger and Ranaldi, 1992; Beninger and Rolfe, 1995; Ranaldi et al., 1995). In contrast, the D2-like agonists bromocriptine and quinpirole dose-dependently enhance the conditioned reward effect (Beninger and Ranaldi, 1992; Ranaldi and Beninger, 1995). That these differential effects of D1-like vs. D2-like agonists bear strong resemblance to the differential effects of direct vs. indirect DA agonists suggests that tonic stimulation of D1-like receptors masks the DA signal that would otherwise be engaged by endogenous DA released during the presentation of conditioned rewards (Beninger and Ranaldi, 1992; Sutton and Beninger, 1999).

While five different D1-like agonists all disrupt the ability of conditioned rewards to control responding, to date, the effects of only two D2-like agonists have been examined. Thus, the present study examined the effects of another D2-like agonist, 7-hydroxy-*N,N*-di-*n*-propyl-2-aminotetralin (7-OH-DPAT), on the acquisition of responding for conditioned reward. 7-OH-DPAT is a D3-preferring (relative to D2) agonist and demonstrates 50–100 times higher selectivity for D3 over D2 receptors in genetically transfected cells (Lévesque et al., 1992), although this figure might be an overestimate when applied to brain tissue (Booth et al., 1994; Lévesque, 1996). Since 7-OH-DPAT exhibits differential selectivity within the D2-like family of DA receptors, its effects on responding for conditioned reward were examined across a full range of doses. For comparison, the effects of the D2-preferring D2-like agonist bromocriptine were also examined.

2. Methods

2.1. Subjects

Treatment of animals in the present study was in accordance with the Animals for Research Act, the Guidelines of the Canadian Council on Animal Care, and relevant university policies, and was approved by the Queen's University Animal Care Committee.

Male Wistar rats ($N = 159$; Charles River Canada), with free-feeding weights of 250–300 g were housed individually in a temperature-controlled environment (21°C) on a 12-h light–dark cycle (lights on at 06:00 hours). Following a period of habituation to the housing environment of at least 5 days, animals' weights were reduced to and maintained at 80% of their free-feeding values, through daily feedings with measured rations.

2.2. Apparatus

Testing was carried out in four similarly constructed operant chambers ($23 \times 29 \times 19$ cm), with aluminum plate sides and clear Plexiglas tops and doors. Within each

chamber, a 4.9-kHz tone generator (Sonalert) was located at a height of 14 cm from the floor, above and between two 2-W light bulbs positioned 8.5 cm apart and 10 cm from the floor. The Sonalert was adjusted to deliver a tone 10 dB above the background noise level. A 2.0×4.0 cm feeder cup, 2.5 cm above the floor, was located in the center of the 23 cm back wall, directly below the tone generator. Two removable levers (7.5×3.5 cm) were positioned in the middle of each 29 cm side wall, depression of which required a force of approximately 0.09 N. Each operant chamber was enclosed in a ventilated sound-attenuating box.

2.3. Procedure

All experimental groups underwent a 13-day experimental protocol, consisting of three phases — preexposure, conditioning, and test — with one day off in between phases.

The preexposure phase consisted of five 40-min sessions with both levers present in the chambers. Depression of one lever produced a tone (3 s) and the other turned the chamber house lights off (3 s). Two chambers had the lights-off producing lever on the right wall and the tone-producing lever on the left, while the other two chambers had the reverse arrangement. The number of responses on each lever was recorded for each of the five sessions.

During the four 65-min conditioning sessions, the levers were removed from the experimental chambers. During each session, the 3-s lights-off stimulus was presented 80 times according to a random time 45-s schedule, i.e., the average interval between stimulus presentations was 45 s (range 3–100 s). In the first conditioning session, each stimulus presentation was followed by delivery of a 45-mg food pellet (Bioserve). During the following three sessions, the lights-off stimulus was followed by food delivery a random 33% of the time. This partial pairing procedure was employed to produce a stronger conditioned reward effect (Knott and Clayton, 1966).

After the last conditioning session, the levers were placed back in the experimental chambers for the test phase. This phase consisted of two 40-min sessions, over which the number of responses made on each lever was recorded. A conditioned reward effect was evidenced by a relative increase in the number of responses made on the lights-off lever in the test phase compared to that of the preexposure phase.

A total of 15 groups were examined. Two groups, one receiving saline ($n = 11$) and the other a Tween-80/distilled water suspension ($n = 14$), were used as vehicle controls for 7-OH-DPAT and bromocriptine, respectively. Nine groups ($n = 11$–14) were given 7-OH-DPAT, in doses of 0.02, 0.06, 0.10, 0.18, 0.25, 0.50, 1.00, 2.50, 5.00 mg/kg, ip, 30 min prior to each test session. Four additional groups ($n = 10$–12) received bromocriptine, in doses of 0.50, 2.50, 3.50, 5.00 mg/kg, ip, 30 min before testing.

2.4. Drugs

(+)-Bromocriptine methanesulfonate [Research Bio-chemicals (RBI), Natick, MA] was suspended in a small amount of polyoxyethylene sorbitan monoleate (Tween-80) and then added to distilled water. ($\pm$)-7-OH-DPAT (RBI) was dissolved in physiological saline. Both compounds were prepared daily, and injected in a volume of 1 ml/kg.

2.5. Data analysis

Only data from the last 30 min of each session were examined because previous studies have demonstrated that the last 30 min provides the most stable estimate of response rates (Hoffman and Beninger, 1985). First, the change in responding from preexposure to test in the control groups was analyzed to confirm that the lights-off stimulus served as an effective conditioned reward (Table 1). In this analy-sis, the number of responses made on each lever during the last 30 min of the five preexposure and two test sessions was averaged for each rat. The ratio of responding in the test vs. the preexposure sessions were then calculated, adding 1.0 to each value to eliminate the influence of small numbers (Winer, 1971), and these ratios were then square-root transformed to preserve homogeneity of variance (Keppel, 1982). The resulting ratios for the tone (NCR) and lights-off (CR) levers were then compared in each control group using a t test to assess whether conditioning resulted in a selective increase in responding on the lever producing conditioned reward (lights-off) relative to a neutral stimulus (tone). In subsequent analyses, the absolute number of responses averaged across the two test sessions were examined. t Tests were used to compare responding at the CR and NCR levers during the preexposure and test phases in the two control groups — these groups were then combined into a single control if there was no significant difference between them. To examine the effect of dose on responding at each lever, data from groups receiving each drug were subjected to separate single factor analyses of variance (ANOVA) for the CR and NCR levers, followed by post hoc Dunnet's t tests. In cases where responding at both levers was altered by a particular dose, the number of responses at each lever for that dose were square-root transformed and compared with controls using a two-way

(Group $\times$ Lever) analysis of variance. A significant inter-action indicated that the particular dose differentially affected responding at the CR and NCR levers.

3. Results

Responding at the CR (lights-off) lever in both vehicle groups increased almost fourfold from preexposure to test (Table 1). In contrast, responding at the NCR (tone) lever was not altered between the preexposure and test sessions in either group. When the square-root transformed ratios of responding on the two levers in the test vs. the preexposure phase were compared, the ratio for the CR lever was significantly higher for both the saline ($t_{10} = 4.87$, $P < .05$) and Tween vehicle ($t_{13} = 3.80$, $P < .05$) control groups. The two vehicle groups demonstrated highly similar responding on both the CR ($t_{24} = 0.61$, $P > .05$; $t_{24} = 0.07$, $P > .05$, for preexposure and test phases, respectively) and NCR ($t_{24} = 1.00$, $P > .05$; $t_{24} = 0.36$, $P > .05$, for preexposure and test phases, respectively) levers, so these groups were combined in further analyses.

The effect of bromocriptine on the CR and NCR levers is shown in Fig. 1. Bromocriptine enhanced responding on the CR lever in a dose-dependent manner ($F_{4,63} = 7.33$, $P < .05$), with both 3.5 and 5.0 mg/kg producing a significant enhancement relative to vehicle (Dunnet's t test, $P < .05$). Bromocriptine also enhanced responding on the NCR lever, and this effect too was dose-dependent ($F_{4,63} = 5.24$, $P < .05$) with both 3.5 and 5.0 mg/kg significantly enhancing responding. However, bromocriptine had a much more pronounced effect on responding at the CR lever. Analysis of the degree to which responding on both levers was augmented by bromocriptine revealed that 5.0 mg/kg differ-entially enhanced responding on the CR lever. This effect was indicated by a significant Group $\times$ Lever interaction in a comparison of responding at the two levers (square-root transformed) in this group relative to controls ($F_{1,34} = 8.79$, $P < .05$). These results indicate that bromocriptine signifi-cantly enhances the acquisition of responding for condi-tioned reward, despite increases in overall responding.

The dose effect of 7-OH-DPAT on responding at the CR lever appeared biphasic (Fig. 2; $F_{9,124} = 4.51$, $P < .05$). At low doses (0.18 and 0.25 mg/kg), responding on the CR

Table 1

Mean ($\pm$ S.E.M.) preexposure and test number of responses, ratio and square-root transformed ratio values, for each lever for the saline and Tween-80/distilled water vehicle groups[a]

Group	n	Preexposure		Test		Ratio		Square root	
		Tone	L-O	Tone	L-O	Tone	L-O	Tone	L-O
Saline	11	6.6 ± 1.0	7.9 ± 1.7	10.7 ± 2.2	30.8 ± 6.6	1.6 ± 0.2	3.8 ± 0.6	1.2 ± 0.1	$1.9 \pm 0.2*$
Tween/DH$_2$O vehicle	14	8.4 ± 1.5	9.1 ± 1.5	9.6 ± 1.9	31.4 ± 6.7	1.2 ± 0.2	3.8 ± 0.7	1.1 ± 0.1	$1.8 \pm 0.2*$

[a] Abbreviations: L-O; lights-off lever.

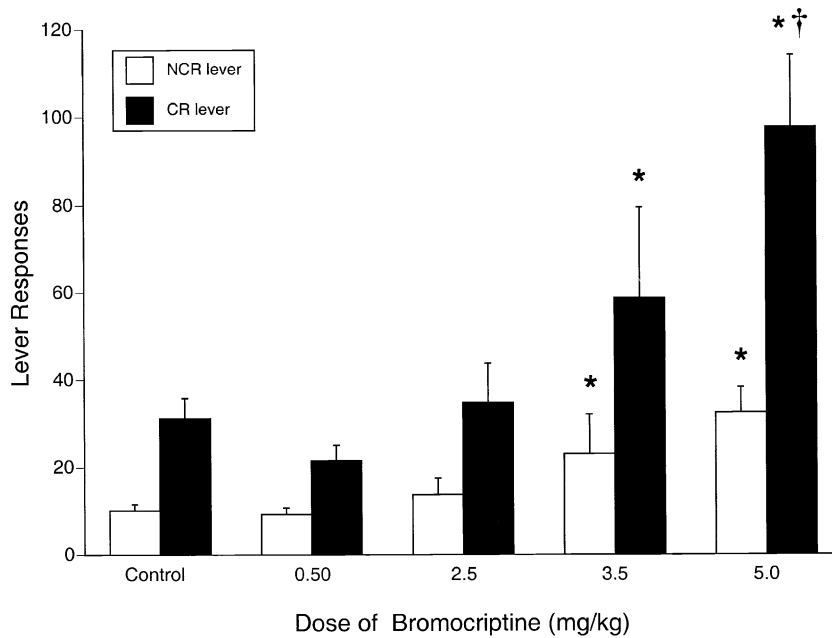* Significantly greater than tone lever in a t test, $P < .01$.

Fig. 1. Mean (+S.E.M.) number of responses made at the NCR (tone) and CR (lights-off) levers during the test phase for groups receiving vehicle or doses of bromocriptine. *Significant ($P<.05$) difference from vehicle; [†]significant ($P<.05$) differential effect on CR lever.

lever during the test was significantly reduced relative to vehicle (Dunnet's *t* test, $P<.05$). At a higher dose of 1.0 mg/kg, responding on the CR lever was significantly enhanced relative to vehicle (Dunnet's *t* test, $P<.05$). At an intermediate dose (0.50 mg/kg), responding at the CR lever was neither enhanced nor impaired relative to vehicle. Responding at the NCR lever was also affected by 7-OH-DPAT ($F_{9,124}=3.67$, $P<.05$). Specifically, at higher doses (1.0–5.0 mg/kg), significant increases in NCR lever responding

were observed (Dunnet's *t* test, $P<.05$). Analysis of responding at both levers revealed that 0.25 mg/kg, relative to vehicle, selectively reduced responding at the CR lever. This effect was indicated by a significant Group × Lever interaction in a comparison of responding at the two levers (square-root transformed) in this group relative to controls ($F_{1,36}=6.26$, $P<.05$). A similar analysis of the degree to which responding on both levers was augmented by 1.0 mg/kg 7-OH-DPAT revealed that 1.0 mg/kg differentially
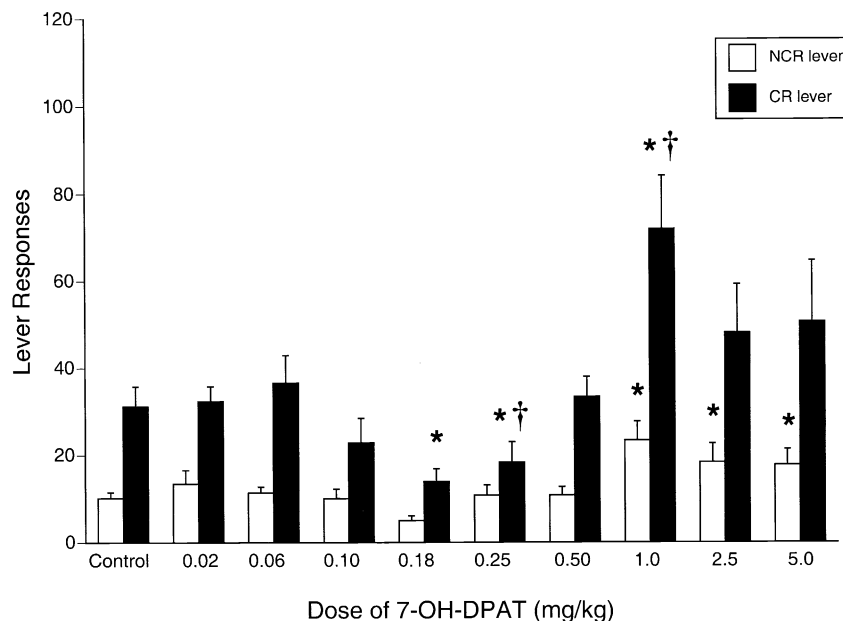

Fig. 2. Mean (+S.E.M.) number of responses made at the NCR (tone) and CR (lights-off) levers during the test phase for groups receiving vehicle or doses of 7-OH-DPAT. *Significant ($P<.05$) difference from vehicle; [†]significant ($P<.05$) differential effect on CR lever.

enhanced responding on the CR lever ($F_{1,36} = 4.10$, $P < .05$). Thus, as with bromocriptine, 1.0 mg/kg 7-OH-DPAT stimulates overall responding but still differentially enhances responding on the CR lever.

4. Discussion

Both vehicle groups responded more on the lever producing conditioned reward (lights-off) from preexposure to test, than on a lever producing a stimulus (tone) with no prior association with reward. Previous research has demonstrated that if the conditioned stimulus is negatively correlated with food (Beninger and Phillips, 1980; Hoffman and Beninger, 1985), or food alone is presented in the conditioning phase (Beninger and Ranaldi, 1992), responding differs little between the preexposure and test phases. Moreover, enhanced responding for a conditioned reward is not specific for either the type of stimulus that is conditioned, or the primary reward used for the pairing. Indeed, turning the chamber lights on or off, a tone, or a compound visual/auditory stimulus can all be effective conditioned rewards when paired with such diverse primary rewards as food, water, or brain stimulation (Beninger and Phillips, 1980; Beninger and Ranaldi, 1992; Knott and Clayton, 1966; Robbins et al., 1983). Thus, consistent with a substantial body of evidence, the selective enhancement of responding on the lights off vs. the tone lever from preexposure to test indicates that the lights off stimulus acquired conditioned rewarding properties as a result of prior pairing of this stimulus with primary reward (food).

Results further indicate that 1.0 mg/kg 7-OH-DPAT differentially enhances responding for conditioned reward relative to a neutral stimulus. Thus, in addition to a significant increase in responding at both the CR and NCR levers indicative of a generalized stimulant effect, responding at the CR lever was differentially enhanced by 1.0 mg/kg 7-OH-DPAT. These results are similar to that observed with the other D2-like agonists, bromocriptine and quinpirole, which also enhance the acquisition of responding for conditioned reward in a dose-dependent fashion (Beninger and Ranaldi, 1992; Ranaldi and Beninger, 1995; present study).

While higher doses (1.0–5.0 mg/kg) of 7-OH-DPAT either enhanced or did not affect the differential responding for conditioned reward, lower doses (0.18 and 0.25 mg/kg) of this drug inhibited the effect in a dose-dependent fashion. Interestingly, the biphasic dose profile of 7-OH-DPAT reported here with responding for conditioned reward is also apparent in other studies examining reward-related learning. For example, studies of conditioned place preference with 7-OH-DPAT have found a dose-dependent place aversion at a range of doses lower than 1 mg/kg (Khroyan et al., 1995), but a significant place preference at a higher dose of 5 mg/kg (Mallet and Beninger, 1994). Moreover, it has been shown that 7-OH-DPAT produces a similar biphasic

effect on responding under progressive ratio schedules for food or intracranial self-stimulation (Depoortere et al., 1996, 1999). Thus, the biphasic dose–response profile of 7-OH-DPAT appears to be a general property of the drug on reward-related learning.

Several explanations could account for the biphasic effect produced by 7-OH-DPAT on responding for conditioned reward and other forms of reward-related learning. Since 7-OH-DPAT is a D3-preferring DA agonist (relative to D2), one possibility is that the differential effects of low and high doses relate to a difference between D3 and D2 receptor activation. D1-like and D2 receptors are found in all major dopaminergic systems, but the D3 receptor appears mostly localized to the brain's limbic regions (Sokoloff et al., 1990). This pattern of distribution suggests that the D3 receptor might play an important role in certain forms of reward-related learning. Central to this type of argument is that the administration of low doses of 7-OH-DPAT should minimize concurrent D2 receptor stimulation; thus, low doses of 7-OH-DPAT could produce a D3-mediated inhibition of conditioned reward that is offset by concomitant D2 receptor activation at higher doses. A finding of particular relevance to this idea is that a selective (albeit partial) D3 agonist has been shown to dose-dependently inhibit responding maintained by conditioned reward in a second-order schedule (Pilla et al., 1999). Moreover, the D3-preferring agonist quinpirole (Sokoloff and Schwartz, 1996) affects conditioned reward in a manner that is quite similar to 7-OH-DPAT. While Beninger and Ranaldi (1992) reported that higher doses of this drug enhance the conditioned reward effect, close scrutiny of their data also reveals that low doses appear to inhibit the effect. These results are consistent with the idea that the inhibition of reward-related learning observed at low doses of 7-OH-DPAT is an effect mediated by D3 receptors. However, an important caveat with respect to this idea is that the in vitro selectivity of 7-OH-DPAT for D3 relative to D2 receptors can vary depending on the assay conditions (see Lévesque, 1996 for discussion); hence, the selectivity of this drug in vivo is still uncertain.

Another possible explanation for the biphasic effect of 7-OH-DPAT (and possibly quinpirole) is that low doses preferentially stimulate autoreceptors, thereby inhibiting DA release that normally accompanies the activation of DA neurons by conditioned rewarding stimuli (Schultz et al., 1997). Previous research has demonstrated that systemic administration of 7-OH-DPAT decreases DA release in the nucleus accumbens (Gilbert et al., 1995), which is consistent with the drug acting, at least in part, at autoreceptors. In addition, 7-OH-DPAT induces several behavioural effects that are consistent with decreases in accumbens DA release. For example, 7-OH-DPAT has been shown to attenuate electrical self-stimulation of the ventral tegmental area (Gilbert et al., 1995) and morphine-induced place preference (De Fonseca et al., 1995), as well as antagonize many spontaneous behaviours related to dopaminergic activity

such as sniffing, grooming, and rearing (De Fonseca et al., 1995; Khroyan et al., 1995).

While these ideas are conceptually distinct, they are not mutually exclusive. Indeed, other behavioral effects of 7-OH-DPAT have been attributed to actions at autoreceptors of the D3 receptor subtype (Gilbert and Cooper, 1995). However, others (Khroyan et al., 1999) have argued that 7-OH-DPAT reduces some DA-mediated behavioral effects by acting on D2/D3 autoreceptors and others by actions at postsynaptic D3 receptors. Since the biphasic profile of 7-OH-DPAT is evident in a number of studies investigating reward, the precise means by which this effect is achieved may provide further insight into functions of D2 and D3 receptors in reward-related learning.

Acknowledgments

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