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# THE DOPAMINE D2 RECEPTOR AGONISTS, QUINPIROLE AND BROMOCRIPTINE PRODUCE CONDITIONED PLACE PREFERENCES

DIANE C. HOFFMAN, PATRICIA R. DICKSON AND RICHARD J. BENINGER

Dept. Psychol., Queen's University, Kingston, Canada

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## Abstract

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1. The conditioned place preference paradigm was used to examine the role of the D2 receptor in mediating the reinforcing effects of dopamine (DA) agonists.
2. During the 3-day pre-exposure phase, rats explored two distinctive end compartments which were adjoined by a small tunnel. During the 8-day conditioning phase, groups of rats were treated with the selective D2 receptor agonists, quinpirole (0.01, 0.025, 0.05, 0.10, 0.25, 1.0 and 5.0 mg/kg IP) or bromocriptine (0, 0.01, 0.1, 0.5, 1.0, 5.0 and 10.0 mg/kg IP) and confined to one compartment for 30 min. On alternate days, rats received vehicle injections and were placed in the opposite compartment. Test days occurred over the remaining 3 days during which untreated animals explored both compartments.
3. Rats conditioned with quinpirole or bromocriptine showed significant increases in time spent in the drug-paired environment from pre-exposure to test indicating the establishment of conditioned place preferences.
4. This suggests a functional role for the D2 receptor in mediating the rewarding effects of DA agonists.

Keywords: bromocriptine, conditioned place preference, D2 dopamine receptors, quinpirole, rats.

## Introduction

The place preference paradigm is useful for studying the reinforcing properties of psychomotor stimulants. After receiving several pairings of a drug injection with a distinctive environment, the drug-free animal shows a relative increase in the amount of time spent in this environment compared to an equally distinctive alternative environment. This shift in preference from pre- to post-conditioning is interpreted as evidence for the reinforcing properties of the drug. Substances (e.g., amphetamine, cocaine and apomorphine) that enhance central dopaminergic transmission are effective in producing place preference conditioning in rats (Mithani et al., 1986; Morency and Beninger, 1987; van der Kooy et al., 1983) and the role of the neurotransmitter, dopamine (DA) in mediating these effects has received considerable support (Bozarth, 1986).

Recently, DA receptors have been divided into at least two functionally distinct

subtypes. According to the nomenclature of Kebabian and Calne (1979), D1 receptors are linked to and stimulate the enzyme, adenylate cyclase, whereas D2 receptors are either unrelated or coupled to its inhibition. The present study investigated the involvement of the D2 receptor in mediating the reinforcing properties of DA agonists. The selective D2 receptor agonists, quinpirole (Fuller and Hemrick-Luecke, 1985) and bromocriptine (Markstein, 1981), were evaluated in the conditioned place preference paradigm. Determining the behavioral profile of bromocriptine is of additional interest because of its effectiveness in the treatment of Parkinson's disease (Lieberman and Goldstein, 1985).

## Methods

Animals. One-hundred and twelve male Wistar rats (supplied by Charles River, Canada) weighed between 225 and 300 g at the start of the experiment. The animals were housed individually in a temperature-controlled (21±1 C) colony room on a 12-hour light(0600-1800 h)/dark cycle and had free access to food and water throughout the study.

Drugs. Quinpirole hydrochloride (Eli Lilly) was dissolved in distilled water and was injected IP in a volume of 1 ml/kg. Bromocriptine mesylate (Sandoz) was suspended in Tween 80 and distilled water and was injected IP in a volume of 1 ml/kg.

Apparatus. The experimental environment consisted of four similar rectangular boxes (84x27x36 cm) constructed of wooden sides and removable Plexiglas covers. Each box consisted of two compartments (38x27x36 cm) joined by a small tunnel (8x8x8 cm); entrance to the tunnel could be blocked by inserting wooden guillotine doors. The compartments differed in brightness, wall pattern and floor texture; in two of the experimental boxes, one compartment was painted brown and had a wire mesh (1 cm squares) floor and the other was painted in vertical black and white stripes (1 cm wide) with a grid (1 cm between rods) floor. In the remaining two boxes, the striped compartment had a wire mesh floor and the brown compartment had a grid floor. The four experimental chambers were located in a dimly lit room. The floors of the boxes were positioned on a fulcrum such that the weight of a rat in one end compartment caused a microswitch to close intiating a timer in another room. Thus, the amount of time the animal spent in each end compartment was recorded.

Procedure. The general procedure was adopted from Mithani et al. (1986). The experimental design consisted of three phases which occurred over 14 consecutive days. The pre-exposure phase involved adapting the rats to the experimental boxes for 15 min on each of three days. With the guillotine doors removed, the rats were placed in a compartment (the start compartment) and allowed to explore the entire box. The choice of the start compartment was counterbalanced across rats and

remained the same for each animal across days. On each of the three pre-exposure days, the amount of time the rat spent in each compartment was measured.

The conditioning phase consisted of eight-30 min sessions. The animals were confined to one compartment by blocking entrance to the tunnel. During four of the conditioning sessions, the rat was pretreated with drug and placed into the nonstart compartment. In the remaining four sessions, the animal received vehicle treatment and was confined to the start compartment. The drug and vehicle pairings occurred on alternate days with the drug pairings on days 1, 3, 5 and 7 and the vehicle pairings on days 2, 4, 6 and 8.

Seven groups of rats (n=8) were administered quinpirole (0.01, 0.025, 0.05, 0.1, 0.25, 1.0 and 5.0 mg/kg) approximately 5 min prior to placement in the nonstart compartment on drug days. The distilled water vehicle was injected on nondrug days. Another six groups of rats (n=8) were injected with bromocriptine (0.01, 0.1, 0.5, 1.0, 5.0, 10.0 mg/kg) 1 h prior to placement in the nonstart compartment. The injections on nondrug days consisted of the Tween 80 and distilled water mixture. A vehicle control group (n=8) which received saline on drug days and distilled water on nondrug days was also included.

The postconditioning test occurred on the remaining three days. The guillotine doors were removed. Untreated animals were placed in the start compartment and allowed to explore the entire box for 15 min. The time spent in each end compartment was recorded.

## Results

The time spent on the nonstart side (i.e., the drug-paired side) on each of the 3 pre-exposure days was averaged together to yield one number representing the pre-exposure phase. Similarly, the test phase score was obtained by averaging the 3 test days. A significant increase in the average time spent on the nonstart side from pre-exposure to test signified the establishment of a conditioned place preference.

Rats treated with saline showed little evidence of conditioning (see Figure 1B). A one-way analysis of variance (ANOVA) was conducted on the average pre-exposure and test scores. The difference was not significant ($p>.05$).

Figure 1A illustrates the average pre-exposure and test scores for the groups treated with quinpirole during conditioning. Conditioning was most evident in the intermediate dose range between 0.025 and 1.0 mg/kg. A two-way ANOVA with one repeated measure (phase) yielded a highly significant phase effect, $F(1,49)=12.41$, $p<.001$. Neither the group effect nor the interaction were significant ($p>.05$). Planned tests of simple main effects were subsequently carried out on the pre- and

post-conditioning scores for each group. Because the phase variable was a repeated measure, separate error terms were calculated for each comparison (see Keppel, 1982, p. 428). The group which received 0.1 mg/kg showed a significant increase, $F(1,7)=9.28$, $p<.025$.

Figure 1B illustrates pre-exposure and test scores for the bromocriptine groups. Rats treated with 0.01 mg/kg showed no evidence of conditioning. An increase in time spent on the conditioning side from pre-exposure to test was evident in the remaining groups. The largest increase occurred in animals treated with the intermediate dose of 1.0 mg/kg. A two-way ANOVA with one repeated measure (phase) revealed a highly significant phase effect, $F(1,42)=13.60$, $p<.001$. Neither the group variable nor the phase by group interaction were significant, ($p>.05$). Simple main effect analyses revealed a significant phase effect in the 1.0 mg/kg group, $F(1,7)=98.96$, $p<.001$.

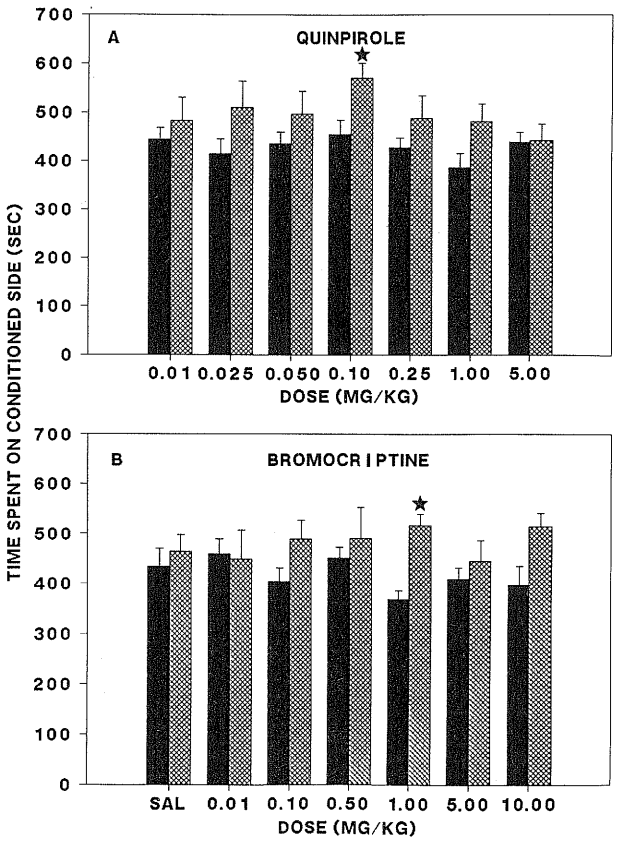


Fig. 1. Average (± SEM) amount of time spent in the drug-paired environment during pre-exposure (solid bars) and test (crosshatched bars) in rats treated with quinpirole (A) or bromocriptine (B).

Animals treated with 0.1 and 10 mg/kg demonstrated an increase which approached significance, $F(1,7)=5.21$, $p<.06$ and $F(1,7)=4.88$, $p<.07$, respectively.

Generally, in groups which showed some evidence of place conditioning the largest effect was observed on the first test day. Thus, to further assess potential dose effects in each drug condition the time spent on the drug-paired side during pre-exposure was subtracted from that on the first test day. These values are summarized in Table 1; the largest difference scores occurred with intermediate doses: 0.1 mg/kg quinpirole and 1.0 mg/kg bromocriptine. Trend analyses revealed a significant quadratic component in those groups conditioned with quinpirole, $F(1,49)=6.99$, $p<.025$, however, neither a linear nor quadratic trend was obtained in the groups administered bromocriptine. The Tukey's Studentized Range test was used to determine if any of the drug doses differed significantly from saline. Because this test provides experimentwise error control, a significant F value from an overall ANOVA is not required prior to its use (Zwick, 1986). None of the quinpirole or bromocriptine doses differed significantly from saline ($p>.05$).

Table 1

Mean (± SEM) difference scores

| Group | Difference score |
|---|---|
| SALINE | 11 (51) |
| QUINPIROLE | |
| 0.01 | 81 (47) |
| 0.025 | 129 (75) |
| 0.05 | 92 (43) |
| 0.1 | 166 (35) |
| 0.25 | 90 (49) |
| 1.0 | 103 (56) |
| 5.0 | 48 (57) |
| BROMOCRIPTINE | |
| 0.01 | 2 (68) |
| 0.1 | 68 (52) |
| 0.5 | 59 (51) |
| 1.0 | 124 (17) |
| 5.0 | 69 (50) |
| 10.0 | 89 (47) |

## Discussion

The overall significant phase effects demonstrated in animals treated with either quinpirole or bromocriptine suggest that these D2 agonists were effective in producing conditioned place preferences. Planned comparisons, however, revealed that only one dose in each drug condition resulted in a significant increase in the amount of time spent on the drug-paired side from pre-exposure to test. Although these effects were highly significant, the fact that the corresponding difference scores did not reliably differ from saline suggests that the conditioning was somewhat weak. These small effects may be related more to the direct- acting properties of these agonists on receptors (in contrast to amphetamine which facilitates DA release and inhibits re-uptake) rather than to their preferential action on the D2 receptor. In this regard, apomorphine, a direct-acting D1-D2 agonist, showed seemingly small conditioned place preference effects over a 1000-fold dose range (van der Kooy et al., 1983). Such comparisons are preliminary given the procedural differences between studies, but the similarity is noteworthy.

The place preference effect observed with quinpirole is consistent with another series of experiments conducted in this laboratory (Hoffman and Beninger, 1987). However, the optimal dose for place conditioning was 1.0 mg/kg, unlike 0.1 mg/kg in the present experiment. The animals were housed individually in the present experiment but in groups in the previous study. Perhaps this variable influenced the differential dose effect, although by what mechanism is unclear. Furthermore, even in the present experiment, there was some evidence of an increase in the amount of time spent on the drug-paired side in rats treated with 1.0 mg/kg. Place preference effects are variable and perhaps a larger group size would result in a significant effect. The present results are also in agreement with the findings of Gilbert et al. (1986) who demonstrated a place preference effect with another selective D2 agonist, N-0437.

The role of the D2 receptor in mediating the reinforcing effects of dopaminergic agonists has received support from self-administration studies. Woolverton et al. (1984) reported that rhesus monkeys readily learned to self-administer D2 agonists but failed to acquire this response for the D1 receptor agonist, SKF 38393.

Although pharmacological studies show that bromocriptine has a high affinity for the D2 receptor (Seeman, 1981), evidence suggests that this drug may also facilitate DA transmission indirectly via presynaptic mechanisms. For example, the locomotor stimulant effect of bromocriptine was antagonized by reserpine and/or alpha-methyl-p-tyrosine pretreatment (Jenkins and Jackson, 1985). This might suggest that the place preference produced by bromocriptine may not be mediated exclusively through D2 receptors. However, previous studies have shown that the D1 agonist, SKF 38393 produces a place aversion (Hoffman and Beninger, 1987). This finding and the

present observation that the D2 agonist, quinpirole produces a place preference suggests that the bromocriptine-induced place preference is not the result of its indirect action.

## Conclusion

Rats treated with the selective DA D2 agonists, bromocriptine or quinpirole, demonstrated significant conditioned place preferences. These results suggest that stimulation of the D2 receptor is involved in mediating the reinforcing properties of psychomotor stimulants.

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Inquiries and reprint requests should be addressed to:

Diane C. Hoffman
Department of Psychology
Queen's University
Kingston, Ontario K7L 3N6