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Bromocriptine enhancement of responding for conditioned reward depends on intact D_1 receptor function

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Abstract It has been suggested that reward-related learning may require intact functioning at the dopamine D_1 receptor. The present experiment tested this hypothesis by challenging the reward-enhancing effects of the D_2 agonist, bromocriptine, with a D_1 antagonist, SCH 23390. For comparison, the effects of the D_2 antagonist, pimozide, were also evaluated. Male rats (n = 240) were pre-exposed to a chamber with two levers, one producing a 3-s lights-off stimulus and the other a 3-s tone stimulus. Four conditioning sessions followed, during which levers were absent and presentations of the lights-off stimulus were paired with food. Testing consisted of comparing presses on each lever after conditioning to before conditioning for each rat. Control groups showed a significantly greater increase in responding for lights-off than tone, indicating that the lights-off stimulus had become a conditioned reward. Results showed that bromocriptine (0.25–10.0 mg/kg, IP, 60 min before test session) enhanced responding at doses of 2.5 and 5.0 mg/kg significantly more on the conditioned reward lever than on the other lever. The lowest dose of SCH 23390 (1.0 μg/kg, SC, 2 h before testing) eliminated the bromocriptine-produced enhancement at 2.5 mg/kg and a significant enhancement was seen at 10.0 mg/kg. The higher doses of SCH 23390 (5.0 and 10.0 μg/kg) eliminated the bromocriptine effect and the conditioned reward effect itself, respectively. The low dose of pimozide (0.1 mg/kg, IP, 4 h before test session) eliminated the bromocriptine-produced enhancement at 2.5 and 5.0 mg/kg and a significant enhancement was now seen at 10.0 mg/kg; the higher dose (0.2 mg/kg) appeared to block the conditioned reward effect itself. These results suggest that both SCH 23390 and pimozide interfered with the reward-enhancing effects of bromocriptine. Thus, the present results suggest that reward-related learning can be enhanced through D_2 receptor stimulation with bromocriptine and that this effect appears to depend on intact D_1 receptor function.

Key words Bromocriptine · Conditioned reward · D_1 receptors · D_2 receptors · Dopamine · Reinforcement · Reward · SCH 23390

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Introduction

Animals can learn to perform a variety of operant tasks to obtain reward. It has been hypothesised that dopamine (DA) plays an important role in this ability of rewarding stimuli to control operant responding (Beninger 1983; Wise and Rompré 1989). This hypothesis has received strong support from studies that used dopaminergic agents in conjunction with behavioural testing. Thus, DA antagonists have been observed to reduce the rewarding impact of food (Wise et al. 1978; Beninger et al. 1987), electrical stimulation of the lateral hypothalamus (Fouriezos and Wise 1976; Gallistel and Karras 1984; Gallistel and Freyd 1987; Stellar and Corbett 1989), intravenously self-administered cocaine (Roberts and Vickers 1984) and sexual contact (Blackburn et al. 1992). Accordingly, DA agonists have been shown to enhance responding for electrical brain stimulation (Herberg et al. 1976; Gallistel and Karras 1984), conditioned reward (Robbins 1975, 1978; Robbins and Koob 1978; Taylor and Robbins 1984; Mazurski and Beninger 1986; Files et al. 1989; Kelley and Delfs 1991; Beninger and Ranaldi 1992), to be self-administered (Pickens and Harris 1968; Pickens and Thompson 1968; Roberts et al. 1977; Goldberg et al. 1981) and to produce preferences for the

environments with which they are paired (Bechara and Van der Kooy 1989; Hoffman and Beninger 1989; Hiroi and White 1991a, b).

Although it is clear that DA plays a role in reward-related learning, the mechanisms by which it does so are not yet well understood. DA receptors can be broadly classified into two families; those which stimulate the enzyme adenylate cyclase are referred to as D_1 and those which are not linked in a facilitative manner to adenylate cyclase are termed D_2 (Niznik and Van Tol 1992; Sibley and Monsma 1992). These families can be further subdivided into several subtypes based on molecular configuration (Niznik and Van Tol 1992; Sibley and Monsma 1992; Gingrich and Caron 1993). Hence, the D_1 receptor family can be separated into D_1 and D_5 receptors and the D_2 family into D_2, D_3 and D_4 receptors. At present, pharmacological agents specific for these further subtypes of DA receptors are not available. Generally, agents previously shown to be relatively specific for D_1 or D_2 receptors similarly affect the other receptors in that family. Therefore, in this paper DA receptors will be referred to as D_1 or D_2.

It has been demonstrated that each receptor subtype participates in reward-related learning. Thus, D_1 and D_2 antagonists reduced the rewarding impact of food (Nakajima 1986; Beninger et al. 1987), electrical self-stimulation (Kurumiya and Nakajima 1988; Nakajima and O'Regan 1991), self-administration of cocaine (Bergman et al. 1990; Corrigall and Coen 1991) and amphetamine-produced place preference (Hoffman and Beninger 1989; Hiroi and White 1991a). D_2 agonists increased the rewarding effect of brain stimulation (Nakajima and O'Regan 1991; Ranaldi and Beninger 1994) and induced a preference for the place with which they were paired (Hoffman et al. 1988; Hoffman and Beninger 1989; White et al. 1991), while D_1 agonists produced a conditioned place preference only when injected directly into the nucleus accumbens (White et al. 1991). It has been suggested that intact functioning of D_1 receptors is necessary for reward-related learning to occur (Miller et al. 1990; Beninger 1992; Beninger and Ranaldi 1992). This hypothesis leads to the prediction that the reward-enhancing effects of D_2 agonists will be antagonised by the administration of a D_1 antagonist. The present experiment tested this hypothesis in a conditioned reward paradigm.

When an animal is exposed to the systematic pairing of a neutral stimulus with a primary reward (e.g., food) the previously neutral stimulus gains control over the animal's behaviour in a manner similar to the primary reward (Bolles 1972; Bindra 1974; Mackintosh 1974). That is, the animal displays approach and other responses toward the previously neutral stimulus; furthermore, that stimulus now can act as a rewarding stimulus in its own right and is termed a conditioned reward. It appears that responding for conditioned reward is dependent on DA transmission (Robbins 1975; Hoffman and Beninger 1985; Mazurski and Beninger 1986; Taylor and Robbins 1986; Kelley and Delfs 1991; Beninger and Ranaldi 1992) similarly to responding for primary reward. We have used the conditioned reward paradigm to demonstrate that the D_2 agonists, bromocriptine and quinpirole, enhanced responding for conditioned reward (Beninger and Ranaldi 1992). We now report the results of an experiment designed to challenge the reward-enhancing effects of the D_2 agonist, bromocriptine (Markstein 1981), with a D_1 antagonist, SCH 23390 (Iorio 1983). The effects of pimozide, a D_2 antagonist (Pinder et al. 1976), on bromocriptine's reward-enhancing effects were also evaluated.

Materials and methods

Treatment of rats 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 policy and was approved by the Queen's University Animal Care Committee.

Subjects

Male Wistar rats (n = 240), obtained from Charles River Canada, weighing between 225 and 275 g (free-feeding) were individually housed in a temperature controlled environment (21 °C) and exposed to a 12-h light/dark cycle (lights on at 0600 hours and off at 1800 hours). Through daily feedings with measured rations all rats were maintained at 80% of their free feeding weight, adjusted for growth.

Apparatus

The experimental environment consisted of four similarly constructed operant chambers. The dimensions were 29 cm in length, 23 cm in width and 19 cm in height. The chambers were constructed of aluminum sides and Plexiglas tops and doors. The floors consisted of aluminum grids. Each chamber was placed in a ventilated sound-attenuating box. Each 29-cm wall of each chamber contained a 7.5 × 3.5 cm^2 removable lever centered at a height of 2.0 cm. A force of approximately 0.09 N was required to depress each lever. At the center of the 23-cm wall was stationed a 2.0 × 4.0 cm^2 feeder cup at a height of 2.5 cm from the floor. Two illuminated 2-W light bulbs (8.5 cm apart) were positioned one on each side of the feeder cup at a height of 10 cm from the floor. Each chamber also contained a 4.9-Khz tone generator positioned at 14 cm from the floor between the two light bulbs and at the center of the 23-cm wall. The tone generator was adjusted to deliver a tone 10 dB above the background noise level.

Procedure

Each group was exposed to an experimental design that consisted of three distinct phases referred to as the pre-exposure, conditioning and test phase. Following is a description of the procedure employed for the paradigm (no-treatment) group. All groups followed exactly the same procedure except that drug groups received their respective doses of bromocriptine or the combination of bromocriptine and SCH 23390 or pimozide prior to each test session, as specified below.

The pre-exposure phase consisted of five 40-min sessions held one per day on 5 consecutive days. Two levers were present in the operant chambers. Depressing one lever produced a tone stimulus lasting 3 s. The other lever produced a lights-off stimulus (lights within the operant chamber were turned off) for 3 s. Two of the chambers had the tone-producing lever on the right wall and the lights-off-producing lever on the left wall; the relationship between side and stimulus was reversed for the other two chambers. Number of responses on each lever was measured for each pre-exposure session.

The conditioning phase consisted of four 60-min sessions held one per day for the 4 consecutive days following the last day of the pre-exposure phase. Both levers were removed from the operant chamber and on each day the rats were exposed to 80 presentations of the 3-s lights-off stimulus according to a random time 45-s schedule. That is, the average time between lights-off stimulus presentations was 45 s. During the first conditioning session each lights-off stimulus was terminated with the delivery of one 45-mg food pellet (Bioserv). During the remaining three conditioning sessions food delivery occurred following a random 33% of the lights-off stimuli. Knott and Clayton (1966) observed that partial pairing resulted in a greater magnitude of conditioned reward than continuous pairing.

The test phase consisted of two 40-min sessions held on the 2 consecutive days following the last day of conditioning. The levers were again present in the operant chamber and the number of responses on each lever was measured. Conditioned reward was observed as a relative increase in the number of responses on the lights-off lever in the test phase compared to the pre-exposure phase.

The paradigm group (n = 26) did not receive any injections prior to testing. The vehicle group (n = 19) received Tween 80 and distilled water (the vehicle for SCH 23390 and bromocriptine; see below) subcutaneously (SC) and intraperitoneally (IP), 2 h and 1 h, respectively, prior to each test session. All of the remaining groups received IP injections of bromocriptine 1 h prior to each test session. Five groups (ns = 8–21) received bromocriptine alone in doses of 0.25, 1.0, 2.5, 5.0 and 10.0 mg/kg. Nine groups (ns = 7–9) received SCH 23390 injected SC 2 h prior to testing plus bromocriptine 1 h prior to testing. SCH 23390 was injected in doses of 1.0, 5.0 and 10.0 μg/kg and each dose was combined with 2.5, 5.0 or 10.0 mg/kg bromocriptine. Six groups (ns = 9–10) received pimozide injected IP 4 h prior to test sessions and bromocriptine 1 h before. Pimozide was injected in doses of 0.1 or 0.2 mg/kg and each dose was combined with 2.5, 5.0 or 10.0 mg/kg bromocriptine.

Drug preparation

SCH 23390 hydrochloride (Research Biochemicals) was suspended in a small quantity of the polymer, polyoxyethylene sorbitan monooleate (Tween 80), and added to distilled water at an appropriate concentration to yield an injection volume of 1.0 ml/kg. Similarly, bromocriptine (Research Biochemicals) was suspended in Tween 80 and added to distilled water to achieve an injection volume of 1.0 ml/kg. Pimozide (Janssen Pharmaceutica) was dissolved in boiling tartaric acid (6 mg/ml) and cooled to room temperature prior to injection in a volume of 1.0 ml/kg.

Data analyses

The data within the last 30 min provided the most stable estimate of pre-conditioning rates. In previous studies (Hoffman and Beninger 1985) the number of responses in each 10-min segment of pre-exposure sessions was analysed and it was found that rates were higher in the first 10 min but did not differ significantly for the three remaining 10-min periods. Therefore, only data from the last 30 min were used for pre-exposure sessions in the analyses of the present results. The number of responses made on each lever during the last 30 min of the five sessions in the pre-exposure phase was averaged for each rat. The number of responses made on each lever during the last 30 min of each session in the test phase was averaged for each rat. Finally, the number of responses on each lever in the test phase was divided by the number of responses on that lever in the pre-exposure phase [adding 1.0 to each value entering into the ratio to reduce the influence of numerically small numbers (see Winer 1971)]. These ratios were square root transformed to normalize their distribution for the purposes of analyses (Keppel 1982). Thus, the data consisted of two numbers for each rat.

To evaluate the conditioned reward effect in the paradigm or vehicle group, a one-way analysis of variance (ANOVA) compared the ratios for each lever. A significantly higher ratio of responding on the lights-off lever than on the tone lever was taken as evidence that conditioned reward had occurred. The results for groups receiving each combination of drugs were subjected to two-way ANOVAs with repeated measures on the lever factor. When a lever effect or a lever by group interaction was seen, the ANOVA was conducted again, this time including the data from the control group. The error term for the interaction from this ANOVA was then used to make interaction comparisons between the control group and each drug group (Keppel 1982). When the ratio for the lights-off lever was greater than the ratio for the tone lever for a drug group and there was a significant interaction of lever and group in the comparison with control, it was concluded that the drug treatment enhanced responding for conditioned reward.

Results

The mean ratios of responding on the lights-off lever were greater than on the tone lever in both the paradigm and vehicle groups, indicating that the lights-off lever acted as a conditioned reward (Table 1). Separate one-way ANOVAs revealed significant lever effects for the paradigm [$F(1, 25) = 6.37$, $P < 0.05$] and vehicle [$F(1, 18) = 4.56$, $P < 0.05$] groups. An ANOVA on the data from the two groups combined revealed a significant lever effect [$F(1, 43) = 10.84$, $P < 0.005$] but no lever by group interaction, indicating that the conditioned reward effect was similar for the paradigm and vehicle groups. Hence, the data from both groups combined were used as the control for the remainder of the comparisons (see Fig. 1A).

Figure 1A shows the ratios of responding for the control and bromocriptine-alone groups. Higher doses of bromocriptine appeared to increase responding specifically on the conditioned reward lever, an observation that was supported by an ANOVA of the bromocriptine data that revealed a significant lever effect [$F(1, 44) = 13.62$, $P < 0.005$]. To determine if the conditioned reward effect in the bromocriptine groups differed from that of the control group the ANOVA was repeated with the inclusion of the control data. The analysis revealed a significant lever by group interaction [$F(5, 88) = 2.33$, $P < 0.05$]. Interaction comparisons revealed that the groups receiving 2.5 and 5.0 mg/kg bromocriptine responded significantly more on the lever producing the conditioned reward than did the control group, suggesting that these bromocriptine groups showed an enhanced conditioned reward effect.

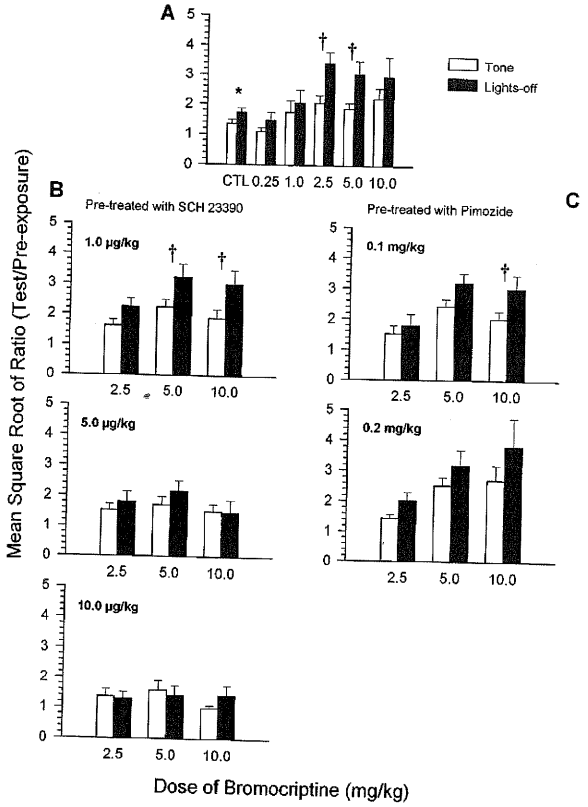

Fig. 1 Mean square root of ratios of responding on each lever in the test phase relative to the pre-exposure phase for all groups. *Vertical bars* represent the standard error of the mean. Lights-off was the conditioned stimulus; tone was the neutral stimulus. Bromocriptine and pimozide were administered IP, 1 h and 4 h before test sessions, respectively. SCH 23390 was administered SC, 2 h before test sessions. *Significant ($P < 0.01$) conditioned reward effect in the control (*CTL*) group; †significant enhancement of conditioned reward effect compared to control group

Similar to the bromocriptine-alone groups the groups receiving the 1.0 µg/kg dose of SCH 23390 showed a profile characterized by enhanced responding on the lights-off lever in comparison to the control group; however, the conditioned reward-enhancing effect of 2.5 mg/kg bromocriptine appeared to be smaller and that at 10.0 mg/kg bromocriptine appeared to be larger (Fig. 1B). The groups receiving 5.0 µg/kg (middle panel, Fig. 1B) and 10.0 µg/kg (bottom panel, Fig. 1B) SCH 23390 failed to show enhanced responding for the conditioned reward lever. In fact, the groups receiving 10.0 µg/kg SCH 23390 failed to show the conditioned reward effect except at the highest bromocriptine dose. The statistical analyses supported these observations.

An ANOVA on the groups receiving 1.0 µg/kg SCH 23390 revealed a significant lever effect [$F(1, 37) = 27.29$, $P < 0.005$]. When the ANOVA was repeated with the inclusion of the control data it revealed a significant lever by group interaction [$F(3, 85) = 3.44$, $P < 0.05$], suggesting that these groups showed a greater conditioned reward effect than the control group. Interaction comparisons located the enhanced conditioned reward effect to the groups receiving 5.0 and 10.0 mg/kg bromocriptine. These analyses suggested that SCH 23390 reduced the conditioned reward effect of the 2.5 mg/kg bromocriptine dose but increased it in the 10.0 mg/kg dose. Hence, the bromocriptine dose-response function was shifted to the right.

An ANOVA on the data from the groups receiving 5.0 µg/kg SCH 23390 revealed a significant lever effect [$F(1, 22) = 13.65$, $P < 0.005$]. However, when the ANOVA was repeated with the control group data included it revealed a significant lever effect [$F(1, 66) = 17.32$, $P < 0.005$], but failed to reveal a significant lever by group interaction. These results support the observation that the 5.0 µg/kg dose of SCH 23390 led to an elimination of the bromocriptine-produced enhancement of the conditioned reward effect.

An ANOVA on the data from the groups receiving 10.0 µg/kg SCH 23390 failed to reveal a significant lever effect. This analysis supported the observation that this dose of SCH 23390 eliminated the bromocriptine-produced enhancement of conditioned reward along with the conditioned reward effect itself.

Both doses of pimozide decreased responding in the 2.5 mg/kg bromocriptine dose but had less effects in the others (Fig. 1C). The highest pimozide dose (top panel, Fig. 1C) appeared to reduce the difference in responding between the levers and to increase the size of the standard errors. These data suggest that the 0.1 mg/kg dose of pimozide may have shifted the curve for the bromocriptine-produced enhancement of responding for conditioned reward to the right. The 0.2 mg/kg dose (bottom panel, Fig. 1C) may have eliminated the enhancement but not the conditioned reward effect itself. These observations tended to find support in the statistical analyses.

Table 1 Mean responding on the lights-off and tone levers in the pre-exposure and test phases and mean square roots of ratios of responding in test sessions divided by pre-exposure sessions for the groups receiving no injection (*Paradigm*) or vehicle injections (*Vehicle*). Values in italics represent the standard error of the mean

Group	Pre-exposure		Test		Square root of ratio	
	Tone	Lights-off	Tone	Lights-off	Tone	Lights-off
Paradigm	5.78	10.04	9.37	25.17	1.33	1.68
	0.8	*1.36*	*1.57*	*3.16*	*0.17*	*0.15*
Vehicle	7.63	13.46	10.39	26.7	1.26	1.62
	1.19	*2.04*	*2.1*	*4.5*	*0.19*	*0.22*

An ANOVA on the groups receiving 0.1 mg/kg pimozide revealed a significant lever effect [$F(1, 27) = 21.38$, $P < 0.005$] without the control group data and a significant lever by group interaction [$F(3, 75) = 2.71$, $P < 0.05$] when the ANOVA was repeated with the control data. Interaction comparisons revealed that the 10.0 mg/kg bromocriptine dose showed an enhanced conditioned reward effect compared to the control group. An ANOVA on the data from the 0.2 mg/kg pimozide groups showed a lever effect that approached significance ($P < 0.07$), suggesting that the conditioned reward effect in these groups was attenuated.

Discussion

The results of the control group indicated that pairing the lights-off stimulus with food pellets resulted in this stimulus acquiring conditioned rewarding properties. Control studies have shown an absence of increased responding for a stimulus that has been negatively correlated (Beninger and Phillips 1980; Hoffman and Beninger 1985) or never paired with food (Beninger and Ranaldi 1992). Additional control studies have shown that pairing the tone with food led to a small nonsignificant conditioned reward effect that was significantly enhanced by amphetamine, showing that stimulant-produced enhancement of responding for conditioned reward is not unique to the lights-off stimulus used here (Beninger and Ranaldi 1992). A conditioned reward effect like that seen in the control group has been observed previously by us (Hoffman and Beninger 1985; Mazurski and Beninger 1986; Beninger and Ranaldi 1992) and others (Bugelski 1938; Skinner, 1938; Stein 1958; Robbins 1975; Cador et al. 1991; Cohen and Branch 1991; Kelley and Delfs 1991).

Bromocriptine doses of 2.5 and 5.0 mg/kg increased responding on the lever producing the lights-off stimulus significantly more than responding on the tone lever. These findings are interpreted as a bromocriptine-produced enhancement of conditioned reward and are in agreement with our previous findings (Beninger and Ranaldi 1992). The 1.0 µg/kg dose of SCH 23390 eliminated the bromocriptine-produced enhancement at 2.5 mg/kg and revealed a significant enhancement at 10.0 mg/kg. This might be seen as a shift to the right in the bromocriptine dose-response function and may indicate an attenuation of the bromocriptine-produced enhancement of conditioned reward. The 5.0 and 10.0 µg/kg doses of SCH 23390 eliminated the bromocriptine-produced enhancement of conditioned reward and the conditioned reward effect itself, respectively. Because all doses of bromocriptine were not affected similarly and because the decreased responding occurred largely on the conditioned reward lever it is unlikely that the effects of SCH 23390 resulted from a simple motor impairment. More likely, this pattern of results suggests that SCH 23390 acted directly to antagonise bromocriptine's reward-enhancing effects and to decrease the conditioned rewarding properties of the lights-off stimulus.

It was found that the lowest dose of pimozide eliminated the bromocriptine-produced enhancement at 2.5 and 5.0 mg/kg and revealed an enhancement at 10.0 mg/kg. This also might be seen as a shift to the right in the bromocriptine dose-response function and might suggest a direct antagonism of the bromocriptine-produced enhancement of conditioned reward. The fact that increasing the dose of bromocriptine to 10.0 mg/kg could reinstate responding to non-pimozide-pretreated levels indicates that the effects of pimozide were likely not simply motoric. The highest dose of pimozide eliminated the bromocriptine reward-enhancing effects but perhaps not the conditioned reward effect itself (this is supported by a lever effect that approached significance at $P < 0.07$). Perhaps a higher dose of pimozide would eliminate the conditioned reward effect.

Bromocriptine has been demonstrated to be self-administered by monkeys (Woolverton et al. 1984) and to produce a conditioned place preference in rats (Morency and Beninger 1986; Hoffman et al. 1988). The reward-enhancing properties of bromocriptine are consistent with the observation of reward-enhancing effects produced with other D_2 agonists (Nakajima and O'Regan 1991; White et al. 1991; Beninger and Ranaldi 1992) and suggest that the D_2 receptor may be involved in reward-related learning. The mechanisms by which D_2 receptor stimulation plays a role in reward are not yet clearly understood. However, there exists evidence that, at least in regards to D_2 receptor mediation of unconditioned behaviour, intact D_1 receptor functioning may be necessary (White et al. 1988). Perhaps D_2 receptor mediated reward also requires intact D_1 receptor functioning.

The 1.0 µg/kg dose of SCH 23390 reduced the effect of bromocriptine at a low dose (2.5 mg/kg) and enhanced it at a high dose (10.0 mg/kg) and the 5.0 µg/kg dose eliminated the bromocriptine-produced enhancement of conditioned reward. These results suggest that SCH 23390 directly antagonised bromocriptine's reward-enhancing effects and provide support for the hypothesis that intact D_1 receptor functioning is necessary for D_2-mediated effects on reward. The 10.0 µg/kg dose of SCH 23390 eliminated the conditioned reward effect itself, a finding which suggests that the ability of the lights-off stimulus to act as conditioned reward depended on the D_1 receptor. It has been hypothesised that reward-related learning occurs through the D_1 receptor (Miller et al. 1990; Beninger 1992; Beninger and Ranaldi 1992). This hypothesis is supported by the present results.

Pimozide has been demonstrated to reduce the rewarding impact of several types of primary (Yokel and Wise 1975; Wise et al. 1978; Gallistel and Karras 1984; Beninger et al. 1987; Fantie and Nakajima 1987)

and conditioned rewards (Beninger and Phillips 1980; Hoffman and Beninger 1985). The present finding that pimozide attenuated bromocriptine's reward-enhancing effects can be explained through its action as a D_2 receptor antagonist (Pinder et al. 1976). Hence, pimozide decreased bromocriptine's effectiveness by displacing it at the D_2 receptor site. Thus, the reward-attenuating effects of the low dose of pimozide (and perhaps that of the high dose also) were surmountable by increasing D_2 receptor stimulation with a higher dose of bromocriptine. These findings add further support for a role of D_2 receptors in reward-related learning.

The present results support the hypothesis that DA transmission is important for reward-related learning to occur (Beninger 1983; Wise and Rompré 1989). By directly challenging the reward-enhancing effects of a D_2-specific agonist with a D_1 antagonist it was possible to investigate the interaction of these two receptor subtypes in reward. The data show that bromocriptine, a D_2 agonist, can enhance responding for conditioned reward and that this enhancement is dependent on intact D_1 receptor function.

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