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Facilitation of efficient search of an unbaited radial-arm maze in rats by D1, but not D2, dopamine receptors

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Abstract

Dopamine (DA) agonists facilitate and antagonists inhibit conditioned preparatory behaviors in rats. We provide added evidence that increased D1 receptor activation facilitates unconditioned preparatory behavior as well, this time in the form of efficient search of an unbaited radial-arm maze. Administration of 0.1, but not 1.0, mg/kg sc SKF81297, a full D1 agonist, increased the number of novel arms chosen in the first eight arms entered. Treatment with 0.1 mg/kg sc D-amphetamine, an indirect DA agonist, also increased search efficiency when given on the first test day but not when given following a test day with a 1.0 mg/kg dose. The 0.1-mg/kg amphetamine-induced facilitation was blocked by coinjection of 0.005 mg/kg SCH23390, a D1 antagonist. Treatment with quinpirole, a D2 agonist, or eticlopride, a D2 antagonist, decreased amount of maze search, but did not affect efficiency. Collectively, our results support the possibility there is a general facilitatory effect of D1 activation on unconditioned preparatory behavior. © 2001 Elsevier Science Inc. All rights reserved.

Keywords: SKF81297; Amphetamine; SCH23390; Quinpirole; Eticlopride; Dopamine; Unbaited radial-arm maze; Unconditioned preparatory behavior

1. Introduction

Manipulation of dopamine (DA) transmission affects some motivated behaviors, but not others. The distinction appears related to a differential involvement of DA in preparatory rather than consummatory behaviors (Blackburn et al., 1989; Sawaguchi and Goldman-Rakic, 1991). Moderate reductions in DA transmission caused by lesions of DA neurons or by administration of DA antagonists, for example, disrupt hoarding and foraging without affecting actual intake of food or water (Blundell et al., 1977; Kelley and Stinus, 1986; Whishaw and Kornelsen, 1993).

Because DA has been linked to learned preparatory behaviors (Berridge and Robinson, 1998; Ikemoto and Panksepp, 1999), it would be useful to establish if manipulations of DA also affect unconditioned preparatory behaviors. Consistent with this view, we have previously shown that treatments that increase D1 receptor activation in rats facilitate unconditioned preparatory behavior directed toward a moving artificial prey stimulus (Tinsley et al., 2000). This effect, however, may be limited to rat predatory behavior rather than apply to preparatory behavior in general (Timberlake, 2001). To test the hypothesis more broadly, we examined the effects of DA manipulations on another unconditioned preparatory behavior, locomotor search of an unbaited radial-arm maze.

Although the radial-arm maze is primarily viewed as a test of spatial memory (Olton et al., 1977), it can also be used to examine unconditioned locomotor search. Research involving a baited radial-arm maze showed that rats typically follow an efficient win-shift strategy, visiting alternative food sources much more readily than they return to previously visited sites (Mogenson et al., 1989). However, subsequent work revealed that food-deprived rats use a similar strategy to search an unbaited radial-arm maze (Timberlake and White, 1990). This finding is in accord with other evidence that rats without food reward perform similarly to rewarded animals in a variety of locomotor tasks that appear to involve search, including a straight-alley (Timberlake, 1983), Dashiell maze (FitzGerald et al., 1985) and radial-arm floor-maze (Hoffman et al., 1999). Because an unbaited, elevated radial-arm maze allows us to distinguish readily

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between efficient search and evoked locomotion, we used this apparatus to examine the effects of DA manipulations on unconditioned preparatory behavior.

The role of DA receptor mechanisms in simple locomotion and learned foraging is well established. Efficient performance of randomly reinforced search behavior, for example, is disrupted by D1, but not D2, antagonists (Floresco and Phillips, 1999). Fink and Smith (1980) also showed that a nonselective DA receptor agonist like apomorphine restored unreinforced open-field locomotion and exploratory behavior after destruction of mesolimbic DA terminal fields. The effect of apomorphine, moreover, was blocked by DA receptor antagonists. Smialowski (1989) demonstrated a D1-selective effect by showing that animals withdrawn from chronic D1 antagonist treatment to increase D1 receptors sensitivity, showed more exploratory behavior than control animals.

In the present study, we tested the effects of a full D1 agonist (SKF81297) as well as amphetamine, an indirect DA agonist. Amphetamine also was tested in combination with SCH23390, a D1 antagonist, to verify D1 involvement. Other animals were tested with a D2 agonist (quinpirole) or a D2 antagonist (eticlopride) to assess a possible role for D2 receptors. To distinguish between drug-induced effects on efficient search and evoked motor activity, we counted the number of novel arms entered during the first eight choices on an unbaited eight-arm maze as well as the total number of arms entered during 5 min. Facilitation of efficient search behavior required an increase in the number of novel arms entered in the first eight choices, rather than simply an increase in total arms entered during the trial.

2. Materials and methods

2.1. Subjects and procedure

We used 60 experimentally naive female Sprague–Dawley Norway rats, aged between 90 and 120 days divided into five treatment groups. All subjects were bred in the departmental animal colony (source animals supplied by Harlan Industries, Indianapolis, IN) and kept under a 12:12 h light–dark cycle with the lights off at 18:00 h. Subjects had ad libitum water and were maintained at 85% of their free-feeding weight by controlling the amount of their single daily meal following the experimental session by 45 min.

Subjects were run on an elevated eight-arm radial maze. The platform and arms were raised 67 cm above the floor. The octagonal central platform measured 14.5 cm on a side and was 34 cm across. The arms were 10 cm wide and 70 cm long. Each arm was enclosed by sidewalls. The right sidewall was 3 cm high. The first 32-cm of the left sidewall was 12 cm high (to prevent jumping from one arm to the next) and the rest was 3 cm high. A 2.5-cm depression (a food cup) was drilled in the end of each arm.

The maze was painted grey and housed in a quiet, unadorned room approximately $3 \times 2.5 \times 2.5$ m high. The room was lit by a 25-W, red-painted bulb housed in a low-reflectance shade set 1.7 m above the center of the maze. A camera set above the maze and connected to a monitor in a neighboring room was used to allow us to score behavior without disturbing the animals.

Animals were food deprived and handled for 6 days before maze exposure. Rats were then run one trial per day for 11 successive days with the first group beginning at approximately 11:00. The start times for each group were rotated daily to avoid session-order effects. The initial 8 days were used to establish baseline performance, while the final 6 days comprised testing. Animals were brought from the colony to the maze room in groups of four. Individual animals were placed on the center of the platform, oriented away from the room door, and allowed to move about the maze for 5 min. At the end of a trial, animals were replaced in the carrier where they waited until each animal in the group had completed the trial. Following completion, the animals were returned to the colony and fed 1 h later. The maze was cleaned between trials using a dilute (1:200) solution of a deodorant/disinfectant (Roccal-D).

During the final 4 days of baseline recording, we habituated the animals to the injection protocol by daily treatment with 1 ml/kg control solution of physiological saline (subcutaneously) 25 min before the session. During testing, the animals were given the control or drug injection 25 min before the session and run as usual.

2.2. Drugs

SKF81297 hydrobromide (Research Biochemicals), D-amphetamine sulfate (Sigma), quinpirole hydrochloride (Sigma), eticlopride hydrochloride (Research Biochemicals) and SCH23390 hydrochloride (Research Biochemicals) were mixed in 0.9% saline solution and administered subcutaneously as the salt. Coinjected drugs were mixed separately and combined by volume immediately before injection.

There were five treatment groups of 12 animals each. Three groups received SKF81297, D-amphetamine or quinpirole at two doses, 0.1 or 1.0 mg/kg. One group was given eticlopride at two doses, 0.01 or 0.1 mg/kg. These treatments and a saline vehicle control were given in partially counterbalanced order across 3 test days. The final test group received 0.1-mg/kg D-amphetamine coinjected with 0.005-mg/kg SC23390 or saline vehicle counterbalanced across 2 days of testing. One animal that consistently failed to enter eight arms during the 5-min session was removed from the eticlopride group prior to testing and a second animal was removed from the quinpirole group due to illness.

The lower doses of SKF81297, amphetamine and eticlopride have been shown to facilitate unconditioned preparatory behavior (Tinsley et al., 2000). SCH23390 blocked the facilitatory effects of amphetamine treatment in the same study. Quinpirole has been shown to have effects on exploratory behavior (Kelley and Stinus, 1986) over the dose range tested.

2.3. Data analysis

We used a mixed-model ANOVA, with dose as a within-subjects factor and order of doses as a between-subjects factor, to assess the effects of D1 and D2 agonists and antagonists on the number of novel arms the animal entered during its first eight-arm entries. Data from animals that did not enter eight arms during the trial were not included for analysis. We used the same mixed-model ANOVA test with the same factors to assess the effects of treatment on locomotor activation, defined as the total number of arms the animal entered during the 5-min test session. Data from all animals were included, regardless of the number of novel arms they entered. We used a two-tailed within-subjects t test to determine the effects of the amphetamine-SCH23390 coinjection treatment.

3. Results

Fig. 1 shows the effects of drug treatments on search efficiency (number of novel arms entered out of the first eight entries for animals that made eight-arm entries), and Fig. 2 shows the effect of drug treatments on the total number of arms entered during the 5-min test session.

Animals treated with the direct D1 agonist SKF81297 showed a significant effect of drug dose in increasing search efficiency [$F(2,16)=9.1$, $P<.01$]. Scheffe tests revealed that the low dose (0.1 mg/kg) produced more novel choices in the first eight-arm entries than either the high dose (1.0 mg/kg) or the saline vehicle. Drug effects were consistent across the order of treatments [treatment order, $F(2,8)<1$; interaction of dose and order, $F(4,16)<1$]. In contrast to its effect on search efficiency, SKF81297 had no significant effect on total arms entered during a 5-min trial [$F(2,18)=1.36$]. Again, drug dose effects were consistent across the order of treatments, producing nonsignificant results for treatment order, $F(2,9)=2.67$, and Dose × Order Order interaction, $F(4,18)=2.29$.

Animals treated with amphetamine showed a significant Dose × Order interaction effect on search efficiency [$F(2,20)=3.84$, $P<.05$]. Scheffe tests revealed that animals receiving the low dose first (0.1 mg/kg) searched the maze with significantly greater efficiency than under the vehicle treatment ($P<.05$). This was not the case, however, for animals receiving the higher dose of amphetamine first

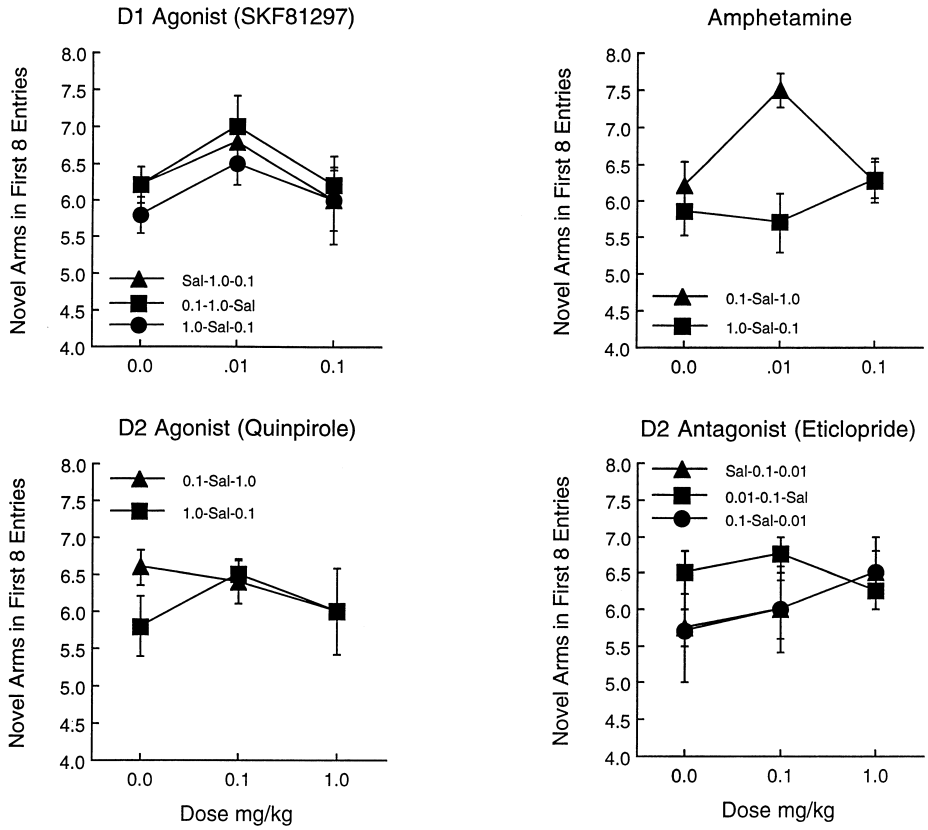

Fig. 1. Drug effects on maze search efficiency as a function of dose. Efficiency is measured by the number of novel arms the animal entered during its first eight-arm entries. Each of the four plots shows the effects of one drug on the mean efficiency at each dose. Data for animals that did not enter at least eight arms at all test doses are not included in this figure. Order of treatment and dose information (mg/kg) for the 3 days of testing is given in the legend. Each line shows the average search efficiency of animals receiving drug doses in the order given by the legend. Error bars show ±S.E.M. Chance performance for this task is 5.3 novel arms entered during the first eight-arm entries.

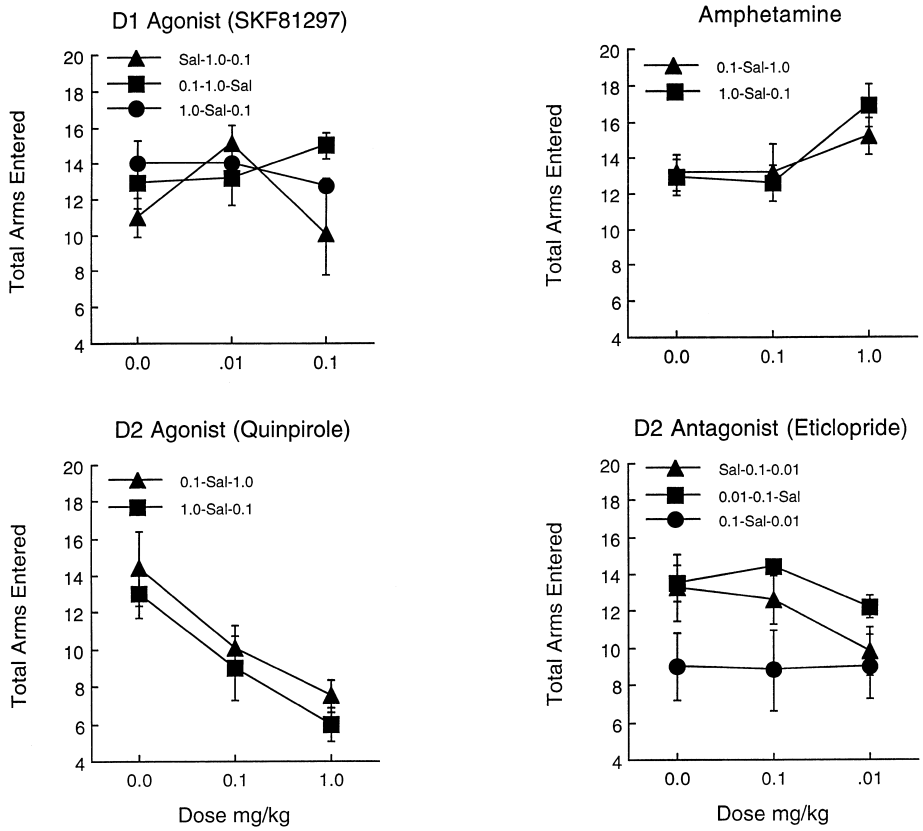

Fig. 2. Drug effects on locomotor activity as a function of dose. Locomotor activity is measured by the average total arms entered during the 5-min test session. Each of the four plots shows the effects of one drug on the mean number of arm entries at each dose. Order of treatment and dose information (mg/kg) for the 3 days of testing are given in the legend. Each line shows the average activity score of animals receiving drug doses in the order given by the legend. Error bars show ± S.E.M.

(1.0 mg/kg). We also found a significant effect of amphetamine dose on total arms entered [$F(2,20) = 4.94$, $P < .05$]. Scheffe tests showed that animals consistently entered significantly more arms after the high (1.0 mg/kg) than the low dose (0.1 mg/kg), $P < .05$.

To test for D1 receptor specificity of search facilitation at the low dose of amphetamine, we injected a group of rats with either a combination of 0.1 mg/kg D-amphetamine and the D1 antagonist SCH23390 or with the saline vehicle, in counterbalanced order. We found no significant difference in search efficiency between the vehicle and coinjection conditions, $t(11) = -0.29$, indicating that search facilitation by the low dose of amphetamine reported above was based on D1 receptor effects. A comparison of the total arms entered during these two conditions also showed no difference, $t(11) = 0.71$, ruling out the possibility that failure to find a difference in search efficiency was due to suppression of locomotion by the D1 antagonist.

In eticlopride treated rats, there was no effect of dose, or a Dose × Order interaction on search efficiency, $F(2,14) < 1$ and $F(4,14) < 1$, respectively. Although there was an overall effect of dose in decreasing total arms entered, $F(2,18) = 3.90$, $P < .05$, Scheffe tests showed no significant differences among specific doses. Quinpirole (0.1 and 1.0 mg/kg) also showed no dose or Dose × Order effect on maze search efficiency, $F(2,4) < 1$ and $F(2,4) < 1$, respectively. The low number of degrees of freedom in these analyses are due to the drug treatment having a significant suppressive effect on locomotor behavior, resulting in fewer animals entering at least eight arms during the 5-min trial [$F(2,18) = 15.5$, $P < .01$]. This suppression effect occurred at both the low ($P < .05$) and high ($P < .05$) doses.

4. Discussion

Our results indicate that facilitation of unconditioned preparatory behavior by D1 agonists applies also to efficient maze search, extending our previous finding of increased predatory behavior (Tinsley et al., 2000). In both cases, moreover, the facilitatory effects occurred at similar drug doses, and did not appear to depend on a general evoked increase in locomotion. It seems possible, therefore, that activation of D1 receptors is relevant for a wide array of, if not all, unconditioned preparatory behaviors.

In the radial-arm maze, our results with the D1 agonist SKF81297 showed that a low dose increased search efficiency but not total arm entries, arguing against a simple facilitation of general locomotor activity. In contrast, treatment with the higher dose had no effect on search, suggesting

that the D1 agonist facilitation of this behavior has an inverted U-shaped function. This hypothesis is consistent with evidence that low doses of a D1 agonist facilitate responding to a lever reinforced with presentations of a secondary reinforcer, but high doses interfere with this discrimination (Beninger and Rolfe, 1995). A likely explanation is that while agonist-induced tonic D1 activation makes responding for the secondary reinforced lever more rewarding, at higher doses the rewarding effects of the drug overwhelmed the differential effects of secondary reinforcer presentation, resulting in a lack of discrimination. Similar effects may be operating in the radial maze. The low dose of SKF81297 may give a novel arm stronger approach-evoking properties, while the higher dose overwhelms this effect, leading to a lack of preference. Nevertheless, the higher dose group entered more novel arms in the first eight than would be predicted by chance, indicating at least some discrimination of novelty remained at this dose.

Treatment with amphetamine showed a similar pattern in animals given the low dose treatment first. Under these conditions, amphetamine resulted in significantly more efficient maze search behavior than vehicle, and with no increase in general locomotion. Additionally, the increase in search efficiency was blocked in a separate group of animals by coinjection of the D1 antagonist, SCH23390, supporting the critical contribution of a D1-based mechanism.

As with the SKF81297-treated animals, the higher dose of amphetamine failed to facilitate search efficiency, although it did elicit more general locomotion. Interestingly, when the higher amphetamine dose was given first, a subsequent low-dose failed to facilitate search behavior or locomotion. This treatment-order effect is difficult to explain but possibly is related to the motor sensitization known to occur with repeated amphetamine injections (Richardson and Gratton, 1996). Although we did not see an increase in total arm entries in the low-dose animals previously exposed to the higher amphetamine dose, motor sensitization to amphetamine can increase head bobbing, rearing, sniffing and other behaviors that might interfere with locomotion (Rebec and Segal, 1980).

The low dose of eticlopride (0.01 mg/kg) had been shown to facilitate unconditioned contact with moving artificial prey stimuli, an effect that may be related to selective blockade of D2 autoreceptors leading to an increase in DA release (Tinsley et al., 2000). Because low-dose treatments with SKF81297 and amphetamine, which facilitate artificial prey stimulus contact, also facilitate maze search efficiency, we also expected similar results with 0.01 mg/kg eticlopride. Failure to find the expected facilitation of maze search with a low-dose suggests that eticlopride does not respond in the same way as SKF81297 and amphetamine to the behavioral demands of these two tasks. Alternatively, facilitation of maze search may involve DA mechanisms in prefrontal cortex where D2 autoreceptors are relatively sparse (Bannon et al., 1982). In this case, low-dose eticlopride would not alter cortical DA release and, thus, would fail to affect maze search.

This latter view is consistent with evidence that D1, but not D2, receptor blockade in prefrontal cortex impairs spatial working memory (Arnsten et al., 1994; Richardson and Gratton, 1996). In fact, cortical D1 receptors appear to play a critical role in a wide array of cognitive functions (Arnsten, 1997). If cortical mechanisms are involved in maze search, as ample evidence suggests (Sawaguchi and Goldman-Rakic, 1991; Watanabe et al., 1998), then a DA component likely involves D1 receptors. It also is interesting to note that free-choice entry into a novel environment increases cortical DA release (Rebec et al., 1997)

If our hypothesis that D1 activation results in increased preparatory behavior is correct, treatment with low doses of a D2 agonist should reduce preparatory behavior because activation of presynaptic D2 autoreceptors should decrease DA efflux. This prediction is consistent with Mogenson and Wu's (1991) finding that treatment with quinpirole, a D2-selective agonist that causes stimulation of presynaptic D2 autoreceptors, reduced locomotor search behavior. Our results, however, do not support this prediction. Quinpirole treatment did not significantly impair maze search efficiency in animals that entered eight maze arms during the trial. Because a substantial minority of our animals tested (11 of 24 across the two test sessions) failed to enter at least eight arms during the test session, Mogenson and Wu's (1991) finding may indicate a decremental locomotor effect of quinpirole, one that reduced their animals' ability, rather than motivation, to search.

The mechanism by which D1 activation affects search behavior may be related to interactions between DA and glutamate in forebrain terminal fields, in particular the hippocampal-accumbal glutamatergic circuit (Mogenson et al., 1989; Floresco and Phillips, 1999; Floresco et al., 1997), either by altering the ability to detect spatial novelty (Usiello et al., 1998) or by modulating the incentive properties of novelty once it has been detected (Burns et al., 1994; Smith et al., 1997). Either of these mechanisms would increase the unconditioned tendency of rats to approach novelty (Barnett, 1963), one manifestation of which would be more efficient maze search.

In summary, the present results showing DA modulation of search efficiency in an unbaited radial maze extend our previous findings (Tinsley et al., 2000) showing a role for D1 receptors in facilitating unconditioned contact with moving artificial prey. The present study shows similar unconditioned effects on maze search efficiency using the same DA agonists, at the same doses. Thus, increased D1 receptor activation may represent a general characteristic of unconditioned preparatory behavior.

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