Selective Effects of Low-Dose D_2 Dopamine Receptor Antagonism in a Reaction-Time Task in Rats

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Operant responses involving a cued discrimination are sensitively disrupted by neuroleptic drugs that block dopamine (DA) receptors in the brain; however, it is not clear which DA receptor subtypes may be involved in these effects. The role of D_1 or D_2 DA receptor antagonists on the execution of a conditioned reaction-time (RT) motor task was investigated in the present study. Rats were trained to release a lever after the presentation of a visual cue within a RT limit to be reinforced by a food pellet. The D_1 receptor antagonist SCH-23390, at doses that significantly decrease the behavioral effects of cocaine, did not impair performance at any dose (5, 10, or 20 μg/kg) injected subcutaneously. In contrast, a selective D_2 receptor antagonist raclopride (50, 100, or 200 μg/kg) induced a dose-dependent increase in the number of incorrect responses (release of the lever over the RT limit) associated with an increase in the RT. The results suggest that the dopaminergic nigrostriatal system, which has previously been shown to be specifically involved in this RT task (Amalric and Koob 1987), appears to be a sensitive site for sensorimotor integration, and that the execution of the conditioned RT motor task may depend preferentially on the activation of the dopaminergic D_2 receptors in this system.
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KEY WORDS: *Dopamine D_1 receptors; Dopamine D_2 receptors; SCH-23390; Raclopride; Reaction-time task; Rat*

The brain dopamine (DA) systems have been implicated in a variety of behaviors including self-administration of psychoactive drugs or in motor control. Neuroleptic drugs that block DA receptors in the brain (Wise 1982) suppress operant responses reinforced with food, brain stimulation, or stimulant drugs. Furthermore, dopaminergic receptor blockade or neurotoxic lesions of the brain DA system also induce motor and cognitive deficits. The subdivision of DA receptors into D_1 and D_2 sites (Kebabian and Calne 1979) on the basis of in vitro physiological and biochemical studies has opened questions as to the functional differences of these two receptors.

Most of the neuroleptic drugs are antagonists at both receptor subtypes. However, the recently developed DA antagonist, raclopride, has a high affinity for the D_2 DA receptor and crosses the blood-brain barrier fairly easily, reaching its peak concentration at about 15 minutes after intravenous injection (Köhler et al. 1985). Raclopride has no effect on the activity of adenylate cyclase, indicating the absence of action on the D_1 receptors (Ögren et al. 1986). On the other hand, the drug SCH-23390 has a very high affinity for the DA D_1 receptor, as compared to its affinity for the D_2 receptor (Billard et al. 1984; Hyttel 1983; Hjorth and Carlsson 1988); SCH-23390 has been shown to suppress numerous DA-stimulated behaviors such as stereotypy or locomotor activity, demonstrating its dopaminergic action (for review, see Clark and White 1987). Using

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specific selective compounds for the D_1 or the D_2 receptor subtypes, many investigators have suggested that D_1 and D_2 receptors may interact with each other in producing a variety of responses, such as hyperactivity, stereotypy, circling, and grooming in rats (Waddington 1986).

Behavioral studies have indicated a role for the mesocorticolimbic dopaminergic system in the mediation of the pharmacological actions of psychomotor stimulants such as amphetamine or cocaine. Dopamine in the nucleus accumbens appears to be involved in the reinforcing and locomotor hyperactivity induced by psychomotor stimulants (Koob et al. 1987; Roberts et al. 1980, 1982; Yokel and Wise 1978; Le Moal and Simon 1991). Whether these behavioral effects are mediated through the activation of D_1 or D_2 DA receptors is still a matter of discussion (Koob et al. 1987; Woolverton and Virus 1989; Nakajima and Baker 1989; Acquas et al. 1989; Hiroi and White 1991). In contrast, the striatum, receiving dopaminergic afferents (the nigrostriatal DA pathway) as well as cortical and thalamic inputs, plays a crucial role in the initiation and the sequencing of conditioned motor acts (for review, see Iversen 1977).

Previous work has shown that destruction of the DA nigrostriatal pathway significantly impaired reaction-time (RT) performance (Amalric and Koob 1987). Furthermore, the blockade of the dopaminergic receptors with a D_1/D_2 receptor antagonist (haloperidol) within the striatum disrupted this RT motor task and increased RTs (Amalric and Koob 1989). The present study was designed to investigate a potential differential role of the two dopaminergic receptors D_1 and D_2 in the execution of the RT motor task. For this purpose, the effects of the D_1 receptor antagonist, SCH-23390, or the D_2 receptor antagonist, raclopride, injected subcutaneously, were measured on the performance of rats trained to release a lever in a food-motivated RT task.

MATERIALS AND METHODS

Thirty-two male albino Wistar rats (Charles River Laboratories) weighing between 160 and 180 g were maintained on a 12-hour light/dark cycle, with lights on at 7 A.M. Rats were deprived of food for 48 hours, then meal-deprived by restricting the amount of food provided to 15 to 17 g per day per rat. This restriction caused no undue stress to the animals and the animals steadily gained weight during the course of the experiment. After the completion of the experiment (2 months) rats' weight ranged from 290 to 390 g.

Procedure

As previously reported (Amalric and Koob 1987) animals are first trained to press down a lever for food reinforcement on a continuous reinforcement schedule (CRF). They are then conditioned to wait for a light-cue stimulus (conditioned stimulus [CS]) during a time period ranging from 0.25 to 1 second occurring at random (Figure 1). To be reinforced by a 45-mg food pellet (Noyes), the rats have to release the lever within 700 msec. Daily sessions ended after 100 trials. The results are expressed as the number of correct responses by session (release of the lever within 700 msec), and the RT was measured for each trial. The RT was the time period measured from the CS onset to the lever release, measured in milliseconds. The number of incorrect responses, either anticipatory (AN) responses (AN is the release of the lever before the CS) or long (LG) responses (LG is the release of the lever after 700 msec, with the RT also measured in milliseconds), were counted separately.

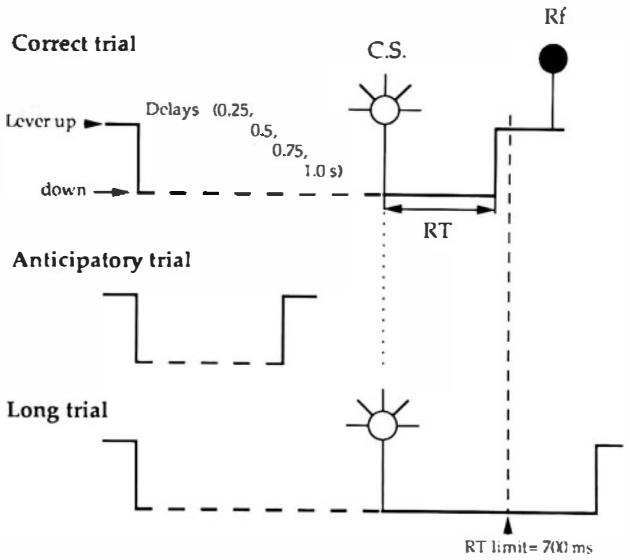

Figure 1. Schematic representation of the RT task procedure. Rats were trained to press a lever down and wait for a visual cue (a light located above the lever). The CS occurs at random after four different delays (0.25 to 1.0 sec). The animals then had to release the lever in a fast movement controlled in a RT. Reaction times were measured as the time period from the CS to the lever release. If the rat failed and released the lever before the CS (AN error), no reward was given and a new trial had to be initiated. If the rat waited for the cue, then released the lever after the RT-limit restriction (700 msec), the trial was also not rewarded. Each correct trial was reinforced with a 45-mg Noyes food pellet and the daily session ended after 100 trials.

Drug Treatment

After stabilization of their performance (1 month), the animals were divided into two groups (n = 16 in each group). On each test day, one group was injected with one dose of a D_1 receptor antagonist (SCH-23390 at 0, 5, 10, or 20 μg/kg, dissolved in NaCl 0.9% [saline]) and

0.1% hydrochloric acid, and the second group with a D_2 receptor antagonist (raclopride at 0, 50, 100, or 200 µg/kg, dissolved in saline vehicle) subcutaneously in a volume of 0.1 ml/100 g. Thirty minutes later all animals were tested in the RT task and their motor performance recorded. The pH of the SCH-23390 solution was readjusted to 6 to 7 with NaOH 0.1 N before each injection. Within each group, each rat was injected four times with all of the different doses tested, using a Latin-square design to control for potential order effects of repeated injection. Between each test day (separated by 2 days) all animals were pretreated with a control injection (NaCl 0.9%) and their performance recorded to test for the potential effect of the handling and injection procedure.

Data Analysis

The number of correct or incorrect (AN, LG) responses as well as RTs for correct and long trials were analyzed separately. Each parameter of the performance, measured before drug treatment (mean of the two control sessions [saline injection] preceding any test day) and during the test day, was subjected to a two-factor analysis of variance (ANOVA), with repeated measures on two factors. The drug groups (doses) constituted the independent factor, the sessions pre- and postdrug were the dependent factor. Individual means between control and drug values were compared using a paired *t*-test.

RESULTS

After training, the performance of the animals was stabilized at a level of mean correct trials by session of 54 for group I (SCH-23390) and 52 for group II (raclopride) (ranging from 21 to 82). The mean correct RT averaged 340 msec (group I) and 342 msec (group II). During baseline, incorrect responses resulted largely from a high number of AN responses (mean number of AN per session was 36 for group I and 38 for group II) rather than from LG responses over the RT limit (mean number of LG per session was 10 for both groups with a mean RT averaging 1500 msec).

The pretreatment with the D_1 DA receptor antagonist (SCH-23390, 5 to 20 µg/kg) did not modify the motor performance at any dose tested (Fig. 2). The animals performed the RT task with the same rate of correct trials as during the control sessions (data not shown).

In contrast, the pretreatment with the D_2 DA receptor antagonist (raclopride, 50 to 200 µg/kg) dose-dependently decreased the number of correct trials. Analysis of variance revealed a significant dose × pre- and posttreatment sessions interaction ($F = 14.16$, $df = 3,45$, $p < .01$). Incorrect responses mainly resulted

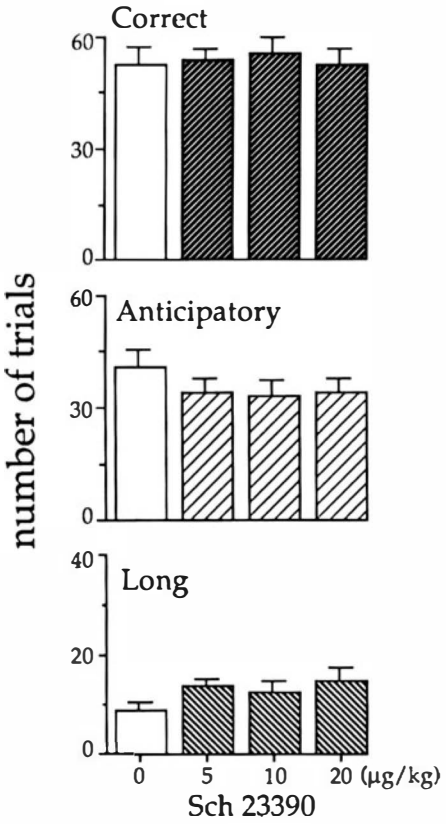

Figure 2. Performance of rats in the RT task, after pretreatment with SCH-23390, injected subcutaneously 30 minutes before the test. A correct trial is a lever release before the RT-limit restriction (700 msec after the CS). An AN error is a release of the lever before the visual CS. An LG error is a release of the lever after the time-limit restriction.

from an increased number of long trials as shown by a significant interaction between dose and sessions (ANOVA: $F = 21.34$, $df = 3,45$, $p < .01$) (Fig. 3). Individual comparisons of means, using a paired *t*-test, showed that the three doses tested significantly increased the number of long trials, as compared to control values. Two of the 16 animals receiving the highest doses did not reach the criterion of 100 lever presses within the session. They stopped pressing the lever after 60 trials and remained in a state of prostration away from the lever. No significant change in the correct RTs (below 700 msec) was observed after raclopride treatment, except with the lowest dose (50 µg/kg). However, the RTs of non-rewarded trials (over 700 msec) were dramatically increased in a dose-dependent manner (ANOVA: $F = 14.10$, $df = 3,45$, $p < .01$) as shown in Figure 4. The RTs were increased up to 2500 msec for the highest dose of raclopride.

DISCUSSION

The present results show that doses of the D_1 receptor antagonist SCH-23390 that significantly decrease the

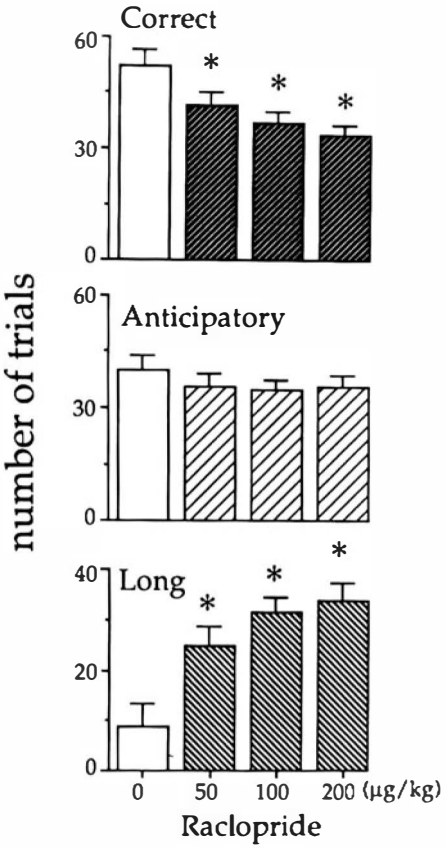

Figure 3. Performance of rats in the RT task after pretreatment with raclopride injected subcutaneously 30 minutes before the test. A correct trial is a lever release before the RT-limit restriction (700 msec after the CS). An AN error is a release of the lever before the visual CS. An LG error is a release of the lever after the time-limit restriction. Asterisks indicate significant difference from control values ($p < .05$, paired t-test) following significant ANOVA.

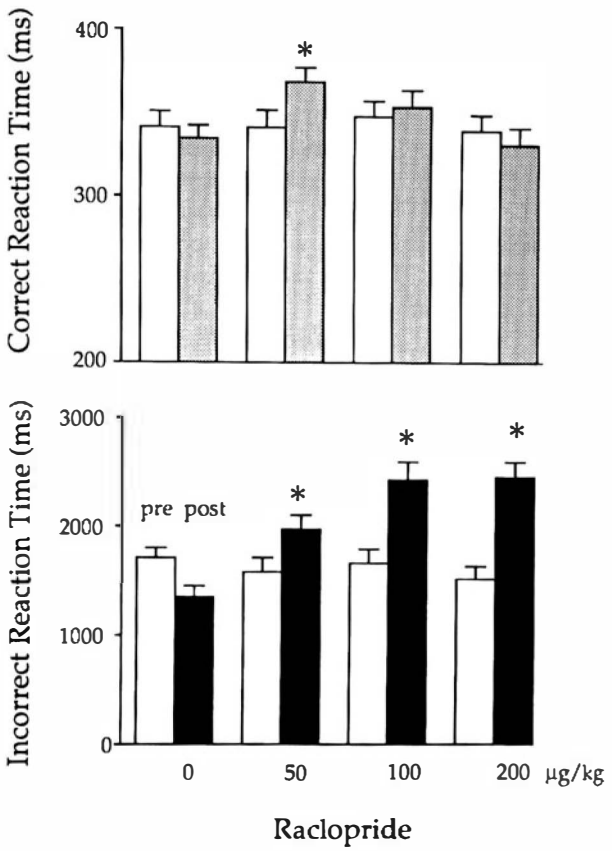

Figure 4. Effect of raclopride pretreatment on RT. Reaction time (in msec ± SEM) was measured from the CS onset to the lever release. Correct RTs occurred before the RT-limit restriction (*top*), incorrect RTs occurred after the RT limit. Asterisks indicate significant difference from control values ($p < .05$, paired t-test, following significant ANOVA).

reinforcing effects or the locomotor stimulation induced by cocaine (Koob et al. 1987; Cabib et al. 1991) and *d*-amphetamine in rats (Mailman et al. 1984) do not impair performance of an appetitive simple RT motor task. However, the selective D_2 receptor antagonist raclopride in doses of 50, 100, and 200 µg/kg induced a dose-dependent disruption of the same task. This disruption was characterized by decreases in the number of correct responses that were wholly attributable to increases in the time to release the lever after the cue.

The ability of raclopride (50 to 300 µg/kg) and SCH-23390 (5 to 20 µg/kg) to produce catalepsy has been tested using the horizontal bar. As previously shown by others, SCH-23390 did not elicit catalepsy at the three doses tested. The ED_{50} to produce catalepsy, calculated by others, was shown to vary between 20 to 80 µg/kg (Morelli and Di Chiara 1985; Meller et al. 1985). Raclopride at low doses (50 and 100 µg/kg) did not produce catalepsy either, whereas higher doses were found to be cataleptogenic (A. Ouagazzal et al., unpublished results). This latter effect could explain the behavior of the two animals that did not complete the full session under the effect of the highest dose of raclopride in the present study. However, it should be stressed that the animals are food-deprived in our behavioral conditions and are thus less sensitive to the hypokinetic effect of raclopride.

The blockade of the D_2 receptors by noncataleptic doses of raclopride in our behavioral situation results in a motor deficit, expressed by an increase in RTs. However, the hypothesis of a possible reduced "reinforcement value" of the food reward cannot be ruled out as it could also result in an impairment of the motor performance. Nevertheless, an "extinction-like" response (increase in the number of lever releases followed by a decrease in performance) would be expected in this case. This was not observed in the present study.

The change in performance induced by raclopride resembles closely the deficits in RT performance previously observed with the mixed D_1/D_2 antagonist α-flupenthixol (Amalric and Koob 1987) and systemic haloperidol (unpublished data). Perhaps more importantly,

this same profile of increases in RT was observed after both DA depletions of the corpus striatum (Amalric and Koob 1987) and intracaudate infusions of haloperidol (Amalric and Koob 1989). A similar increase in operant response duration was observed by others after systemic injections of haloperidol at low doses (Liao and Fowler 1990; Fowler et al. 1986; Meck 1986). These motor deficits in response initiation resemble the symptoms of Parkinson's disease and presumably reflect an impairment of DA transmission within the striatum resulting in extrapyramidal motor effects. Thus it appears that systemic injection of low doses of raclopride can effect a blockade of DA function sufficient to block RT performance, a task mediated by the nigrostriatal DA system.

There is some evidence from neurochemical studies that D_2 antagonists at low doses may preferentially affect the nigrostriatal system. It is striking to note that tritiated ligands of the same DA antagonists used in the present study show that there is a higher relative binding of raclopride in the corpus striatum (Köhler et al. 1985) and a higher relative binding of SCH-23390 in the nucleus accumbens in the rat (A. Pert, personal communication). Furthermore, autoradiographic studies have also revealed a lateral to medial gradient of D_2-receptor density in the rat striatum (Joyce et al. 1985), which corresponds to anatomical and biochemical differences in the striatum, such as a higher cholinergic activity in the lateral striatum. This acetylcholine-rich lateral part of the striatum also receives a cortical innervation from the sensorimotor cortex. Altogether, these results suggest a direct relationship between the D_2 receptors and sensorimotor functions of the striatum (Joyce et al. 1985), although a difference in the relative density of the D_1 and D_2 receptors, as demonstrated by binding studies in different brain structures, does not necessarily imply a functional role.

A preferential involvement of D_2 agonists or antagonists in the expression of nigrostriatal dopaminergic functions is also supported by behavioral experiments. Infusion of a D_2 DA receptor agonist, quinpirole, intracerebroventricularly into rats with 6-hydroxydopamine (6-OHDA) lesions of the midbrain DA system produces more stereotyped behavior than intracerebroventricular infusions of a D_1 agonist, SKF-38393, and conversely intraaccumbens infusions of SKF-38393 were more effective than quinpirole in eliciting locomotor activity in these rats (Breese et al. 1987). Similar results have been seen with microinjections of SKF-38393 and quinpirole into the ventrolateral striatum (Delfs and Kelley 1990). Consistent with these observations, SCH-23390 has recently been shown to block the hyperlocomotion produced by cocaine, whereas selective D_2 antagonists only blocked cocaine-induced locomotion at hypokinetic doses (Cabib et al. 1991).

Clearly, the impairment of the RT task controlled by dopaminergic activity in the corpus striatum would be dependent on the dose of the drugs employed. Higher doses of SCH-23390 clearly produce pronounced motor disturbances and catalepsy (Ioro et al. 1983; Creese and Chen 1985; Hjorth and Carlsson 1988), and animals will completely stop responding in any operant situation. In contrast, lower doses of SCH-23390 within the same dose range as tested in the present study have been found to selectively reverse DA-mediated behaviors, known to involve mesolimbic DA hyperactivity. For example, SCH-23390 (3 to 20 μg/kg) significantly reduced the stimulant effect of cocaine on locomotion (Cabib et al. 1991) and the hyperlocomotor activity following apomorphine injection in rats with 6-OHDA lesion of the mesolimbic terminals in the nucleus accumbens (Amalric et al. 1987; Mailman et al. 1984). Furthermore, the rewarding properties of psychostimulants (cocaine and *d*-amphetamine), which are thought to reflect an activation of the mesolimbic DA system, are also blocked by low doses of SCH-23390 (5 to 40 μg/kg) (Koob et al. 1987; Hiroi and White 1991).

The possibility of selectively affecting a given function of the striatal or mesolimbic DA system by systemic injections of a selective receptor subtype antagonist has important implications for the therapeutic use of these compounds. For example, there is some evidence to suggest that chronic treatment with D_1 antagonists does not produce the acute extrapyramidal syndrome observed with D_2 antagonists (Coffin et al. 1989). Thus at the low end of the dose-effect functions it may be possible to selectively access the function of the nigrostriatal or mesolimbic systems and affect their respective therapeutic effects.

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