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Bidirectional Effects of Dopamine D_2 Receptor Antagonists on Responding for a Conditioned Reinforcer

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SMITH, J. K., J. C. NEILL AND B. COSTALL. *Bidirectional effects of dopamine D_2 receptor antagonists on responding for a conditioned reinforcer.* PHARMACOL BIOCHEM BEHAV **57**(4) 843–849, 1997.—In general, the administration of dopamine (DA) antagonists has been shown to result in the attenuation of reward processes. Recently, however, it has been suggested that low doses of DA antagonists can enhance the incentive value of a primary reinforcer. The present study examined the effect of DA receptor antagonists on responding for a conditioned stimulus (CS) and compared their effects to that produced by *d*-amphetamine. For 12 days, food-deprived rats were trained to associate a CS with a food reward. In the test phase, the CS was presented following a response on one of two levers (CR), whereas responding on the other lever (NCR) had no consequence. Low doses of *d*-amphetamine (0.5 mg/kg), sulpiride (4 mg/kg), pimozide (0.025 mg/kg), and raclopride (0.05 mg/kg) selectively enhanced responding on CR. A low dose of haloperidol (0.01 mg/kg) led to a nonspecific increase in lever responding. Treatment with larger doses of these compounds as well as with the D_1 antagonist SCH23390 attenuated responding on CR. Both CR and NCR responding were reduced following administration of higher doses of *d*-amphetamine. Results indicate that responding for a conditioned reinforcer is potentiated following administration of low doses of D_2 receptor antagonists, suggesting that D_2 receptor blockade can facilitate incentive motivation. © 1997 Elsevier Science Inc.

Conditioned reinforcement Dopamine receptor antagonist Rat D_1 receptors D_2 receptors Reward

EVIDENCE for the importance of dopamine (DA) neurotransmission within the nucleus accumbens in the mediation of reward-related behaviour is derived from studies of the effects of dopaminergic manipulations on responding for a conditioned stimulus (2,7,20,22,33,37). A conditioned stimulus (CS) may be defined as any motivationally neutral stimulus that acquires incentive properties through predictive associations with a primary reinforcer such as food (25), and such stimuli can themselves exert control over responding. The capacity of stimuli to act as reinforcers can be tested by evaluating the control over behaviour by a CS in the absence of the primary reinforcer (13).

One paradigm for studying conditioned reward involves the use of an operant chamber containing two levers. Following a conditioning phase consisting of classical pairings of a compound stimulus with food in the absence of levers, food-deprived rats have been shown to respond more highly on the lever resulting in presentation of the CS than on the lever resulting in presentation of an unpaired stimulus or no stimulus (13). Pairings of a compound stimulus with food (4,6,11), water (23,24,25,33,37), or sex (8) result in an increase in responding on the lever resulting in presentation of the CS. This effect is not observed when food and lights are negatively (11) or randomly (23,33) correlated during the conditioning phase.

The administration of psychomotor stimulants, including amphetamine (6,14,20,25), cocaine (18), and pipradol (4,6,23,25), leads to a selective enhancement in responding for a CS. Both D_1 and D_2 receptor agonists enhance responding on the lever resulting in presentation of the CS, thus treatments with the dopamine D_2 receptor agonists bromocriptine (6,7,22) and quinpirole (6,7,20,37) and with the D_1 receptor agonist SKF38393 (7,20,37) have been shown to selectively potentiate responding for a conditioned reinforcer in rats.

The administration of D_1 and D_2 receptor antagonists has

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also been shown to result in a blockade or attenuation of responding for a CS (11,37). In addition, treatment with D_1 and D_2 receptor antagonists has been shown to result in an intrasession decline in responding for brain stimulation reward (17), and both the D_1 receptor antagonist SCH23390 and the D_2 receptor antagonist pimozide have been shown to suppress appetitively motivated instrumental responding for cocaine, water, and food reinforcement (5,9,12,21,27,38). Results with dopamine antagonists therefore suggest that blockade of DA neurotransmission reduces the motivational properties of rewarding stimuli (1).

Results to date indicate that treatment with DA receptor agonists enhances, whereas administration of dopamine receptor antagonists attenuates, reinforcement processes, both via an involvement of D_1 and/or D_2 receptors. However, there is some evidence to suggest that the administration of DA receptor antagonists may also lead to an enhancement of reward-related behaviour. Recent behavioural studies have indicated that the administration of D_2 and D_3 receptor antagonists can enhance motor performance; thus, locomotor activity is stimulated following treatment with the DA autoreceptor antagonist (+)AJ76 (32). In addition, administration of low doses of selected neuroleptics increased the length of time spent in the food-paired compartment of a conditioned place preference paradigm (10), and sulpiride treatment has been found to enhance amphetamine-induced stereotypy and other DA-dependent behaviours (26). It has been suggested that the ability of these neuroleptic compounds to enhance locomotor activity and reward-related behaviour either results from a selective blockade of D_2 autoreceptors without an impairment of the action of DA on postsynaptic sites, or occurs via a subpopulation of postsynaptic D_2 receptors (29,30,34). Thus, it would appear that stimulation of the dopaminergic system through the blockade of D_2 receptors, as well as stimulation of D_1, D_2, and possibly D_3 receptors, leads to an activation of reward mechanisms.

There is, therefore, evidence to suggest that blockade of D_2 receptors may lead to an increase in reward mechanisms as measured within a conditioned place preference paradigm (10). Operant studies to date have identified a role for activation of D_1 and D_2 receptors in the enhancement of conditioned reward and for D_1 and D_2 receptor antagonism in attenuation of responding for conditioned reinforcement. No studies to date have attempted to increase responding for conditioned reward by means of antagonism at DA receptors. It was the aim of the present series of experiments to investigate the possibility that antagonism at D_2 receptors may lead to enhanced responding for conditioned reward as measured within an operant paradigm. Thus, the present study examined the effect of a wide dose range of the relatively selective D_2 receptor antagonists sulpiride, raclopride, and pimozide, the nonselective DA receptor antagonist haloperidol, and the D_1 receptor antagonist SCH23390 on responding for a conditioned reinforcer, and compared the effects of these compounds with those of the psychomotor stimulant and DA-releasing agent amphetamine. In addition, the effects of all compounds on responding on the inactive lever (NCR) were examined to detect any nonspecific changes in lever pressing activity.

METHODS

Subjects

Thirty female Lister Hooded rats (Bradford University, UK), weighing 250–300 g at the start of experiments, were used as subjects. Animals were housed in groups of five or six and maintained on a 12h L:12h D cycle (lights on at 0700 h). Rats were maintained at 90% of their free-feeding body weight by daily feeding of a measured food ration; water was available ad lib. All experiments were carried out between 0830 and 1300 h.

Apparatus

Both training and testing were carried out in one of four identical operant chambers constructed in-house; every animal was tested in the same chamber throughout. Each chamber contained two retractable levers located 5 cm from the grid floor and 11.5 cm apart, which were positioned on either side of a hinged Plexiglas panel that provided access to 45 mg Noyes pellets (P. J. Noyes Company Inc., Lancaster, UK). The force required to produce a switch closure was 12 g for both levers. All chambers were illuminated by a 12 W house light placed centrally on the ceiling, and two red light emitting diodes (LEDs) were positioned centrally 4.6 cm above each lever. The chambers were housed in sound-attenuated boxes, and external noise was masked by ventilating fans mounted on the side of each box. Boxes were controlled and data collected using Med-PC software (Version 2.0, Med Associates Inc., Lafayette, IN, USA).

Training

Thirty rats were habituated to the operant boxes by the delivery of a food pellet every 30 s over a 20 min period before training began. Rats were then trained to associate a compound stimulus with the delivery of a food pellet. The compound CS consisted of the house light being turned off, the two red LEDs above each lever being turned on, and the characteristic sound of activation of the pellet feeder, which accompanied pellet delivery. Over 10 days, this stimulus was presented for a duration of 1 s every 30 s for a total period of 20 min, with the levers retracted. This period of continual reinforcement was followed by 2 days of intermittent reinforcement, where pellet delivery accompanied presentation of the CS only one in three times, in order to achieve more durable responding (39).

Testing

In the test phase, two levers were introduced into the chamber. One lever was assigned as the conditioned reinforcement lever (CR) and the other as the nonconditioned reinforcement lever (NCR). For half the rats the CR was randomly assigned as the left lever whereas for the remaining rats the CR was the right lever, thus preventing a position preference from influencing the results. Responding on the NCR was recorded but had no programmed consequence; responding on the CR resulted in presentation of the compound stimulus, with the exception that no pellets were delivered due to the removal of the delivery tube. Test sessions were carried out for a period of 30 min, during which time responding on both levers and the number of CS presentations were recorded. Responding for a conditioned reinforcer was subsequently examined following administration of *d*-amphetamine (0.25–1.0 mg/kg), sulpiride (2–32 mg/kg), pimozide (0.025–0.25 mg/kg), raclopride (0.01–5.0 mg/kg), haloperidol (0.01–0.25 mg/kg), and SCH23390 (0.001–0.05 mg/kg) or the appropriate vehicle. Test sessions were separated by at least 2 drug-free days, and a training session was conducted on the day immediately preceding each drug treatment test.

Drugs

d-Amphetamine sulphate (Sigma Chemical Co., Poole, UK) and raclopride tartrate (Research Biochemicals International) were dissolved in 0.9% NaCl. Sulpiride (Sigma Chemical Co.) was dissolved in a small quantity of lactic acid before dilution with 0.9% NaCl and subsequent pH adjustment with 1 M NaOH. Haloperidol was made up in 0.9% NaCl from a 2 mg/ml stock solution (Serenace). SCH23390 (Research Biochemicals International) was dissolved in a small quantity of the polymer polyoxyethylene sorbitan mono-oleate (Tween-80) before dilution with distilled water. Pimozide (Sigma Chemical Co.) was dissolved in 0.3% tartaric acid. All drugs were injected IP (or SC for SCH23390) in a volume of 1 ml/kg 30 min before testing, with the exception of SCH23390 and pimozide, which were administered 2 h and 1 h prior to testing, respectively. A wide range of doses was tested for each drug, similar to those used by Guyon and colleagues (10), to allow both potentiation and attenuation of responding to be examined.

Statistical Analysis

Total responses on the CR and NCR were subjected to square root transformation to preserve homogeneity of variance (36) before being analysed using a two-way analysis of variance (ANOVA) with one between-factor variable (drug dose) and one within-factor variable (lever). The nature of any drug effects on lever responding was evaluated using a one-way ANOVA performed on both CR and NCR responding followed by post hoc analysis using Dunnett's *t*-test.

RESULTS

Amphetamine

As shown in Figure 1, the administration of *d*-amphetamine significantly affected responding on both CR and NCR. A two-way ANOVA revealed a main effect of drug [$F(4, 25) = 17.0$, $p < 0.001$] and lever [$F(1, 25) = 101.8$, $p < 0.001$], as well as a drug × lever interaction [$F(4, 25) = 17.2$, $p < 0.001$]. Post hoc analysis using Dunnett's *t*-test following a one-way ANOVA performed on both CR and NCR responding showed that the administration of a relatively low dose of *d*-amphetamine (0.5 mg/kg) led to a selective and significant increase in CR responding ($p < 0.01$), whereas administration of higher doses (0.75, 1.0 mg/kg) significantly reduced CR responding ($p < 0.05$–0.01). NCR responding was significantly reduced following treatment with a dose of 0.75 mg/kg *d*-amphetamine ($p < 0.01$) to a level below that observed following treatment with saline (Fig. 1).

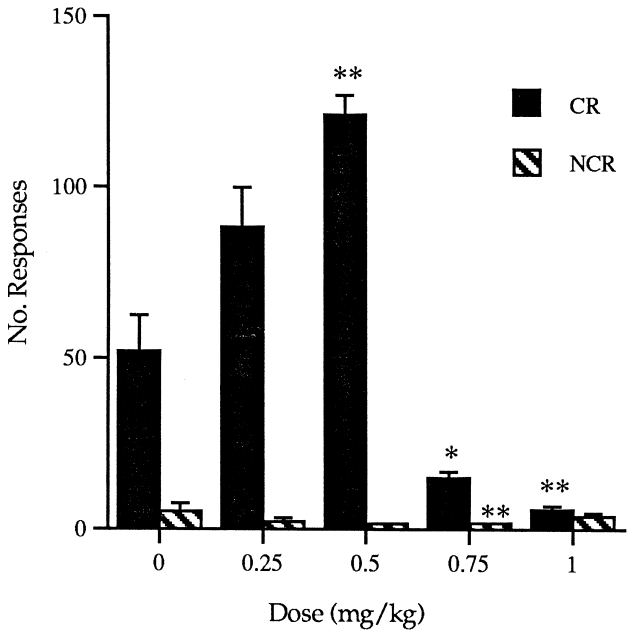

FIG. 1. Effect of *d*-amphetamine (0.25–1.0 mg/kg IP, 30 min prior to testing) on responding for a conditioned reinforcer ($n = 6$ subjects per group). Data are shown as mean ± SEM square root of responses on CR (conditioned reinforcement lever) and NCR (nonconditioned reinforcement lever) over a 30 min test period. Significant effect of drug compared with vehicle treatment on CR responding: $*p < 0.05$, $**p < 0.01$; and NCR responding: $††p < 0.01$ (Dunnett's *t*-test).

Sulpiride, Raclopride, and Pimozide

Figure 2 shows responding on both CR and NCR following treatment with sulpiride. A two-way ANOVA revealed a significant main effect of drug [$F(4, 25) = 5.3$, $p < 0.01$], a significant effect of lever [$F(1, 25) = 105$, $p < 0.001$], and a drug × lever interaction [$F(4, 25) = 5.3$, $p < 0.01$]. To evaluate the nature of the drug × lever interaction, two successive one-way ANOVAs were performed on CR and NCR responding. Post hoc analysis revealed that the number of responses on CR was significantly enhanced following administration of a low dose of sulpiride (4 mg/kg, $p < 0.01$), and a significant reduction in CR responding was observed following treatment with the highest dose of sulpiride (32 mg/kg, $p < 0.05$). No significant effect on NCR responding was observed.

Similarly, treatment with pimozide also significantly affected responding for a conditioned reinforcer (Fig. 3). A two-way ANOVA revealed a significant main effect of lever [$F(1, 25) = 257.9$, $p < 0.001$] and drug [$F(4, 25) = 6.8$, $p < 0.001$] as well as a drug × lever interaction [$F(4, 25) = 5.1$, $p < 0.01$]. A one-way ANOVA performed on CR responding showed a significant enhancement of responding on CR following treatment with a dose of 0.025 mg/kg pimozide ($p < 0.01$) and a significant attenuation of CR responding following injection of a dose of 0.25 mg/kg ($p < 0.01$). NCR responding was not significantly affected by pimozide treatment.

The effect of raclopride administration is shown in Figure 4. As was observed following treatment with both sulpiride and pimozide, a two-way ANOVA revealed a significant main effect of both lever [$F(1, 25) = 128.4$, $p < 0.001$] and drug [$F(4, 25) = 9.8$, $p < 0.001$], as well as a lever × drug interaction [$F(4, 25) = 6.3$, $p < 0.001$]. A one-way ANOVA performed on CR responding revealed a significant enhancement of responding following treatment with a dose of 0.05 mg/kg ($p < 0.01$) and a significant reduction in CR responding following administration of a dose of 5 mg/kg raclopride ($p < 0.01$). A one-way ANOVA performed on NCR responding showed that administration of raclopride had no significant effect on this measure.

Haloperidol

The effect of treatment with haloperidol on responding for a conditioned reinforcer is shown in Figure 5. A two-way ANOVA revealed a significant main effect of drug [$F(4, 25) = 12.6$, $p < 0.001$] and lever [$F(1, 25) = 34.6$, $p < 0.001$], but no drug × lever interaction [$F(4, 25) = 1.3$, NS]. A one-way

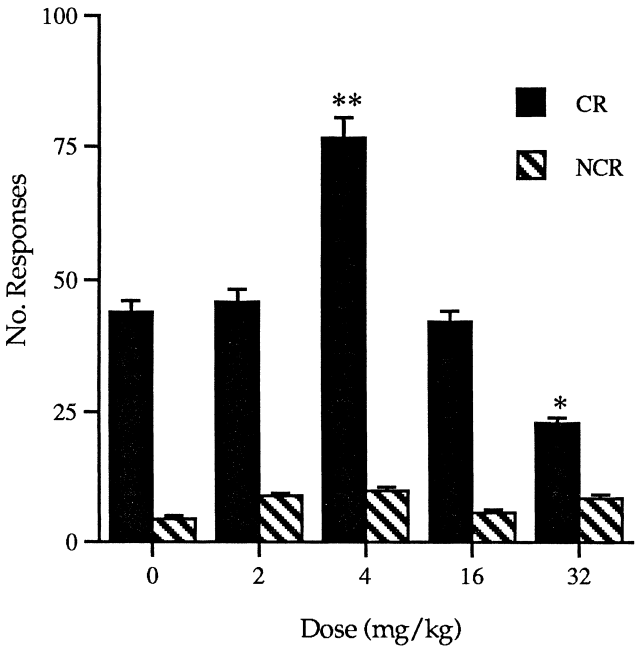

FIG. 2. Effect of sulpiride (2–32 mg/kg IP, 30 min prior to testing) on responding for a conditioned reinforcer (n = 6 subjects per group). Data are shown as mean ± SEM square root of responses on CR (conditioned reinforcement lever) and NCR (nonconditioned reinforcement lever) over a 30 min test period. Significant effect of drug compared with vehicle treatment: $*p < 0.05$, $**p < 0.01$ (Dunnett's t-test).

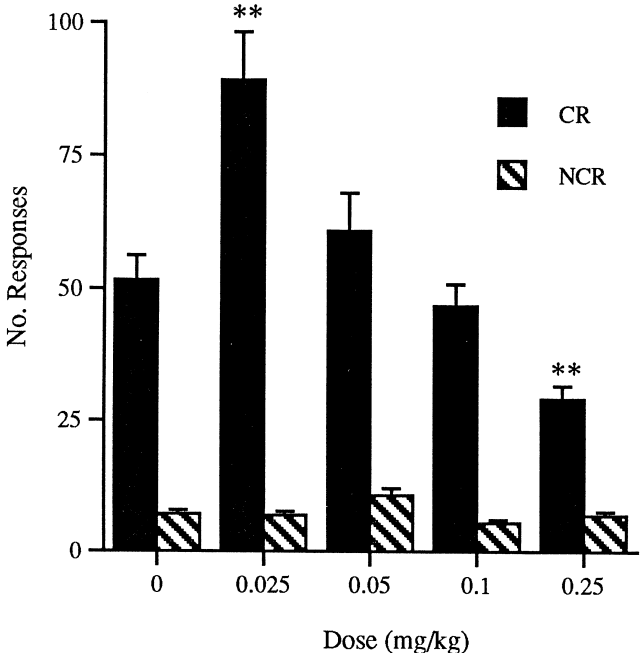

FIG. 3. Effect of pimozide (0.025–0.25 mg/kg IP, 60 min prior to testing) on responding for a conditioned reinforcer (n = 6 subjects per group). Data are shown as mean ± SEM square root of responses on CR (conditioned reinforcement lever) and NCR (nonconditioned reinforcement lever) over a 30 min test period. Significant effect of drug compared with vehicle treatment: $**p < 0.01$ (Dunnett's t-test).

ANOVA followed by post hoc analysis showed a significant effect following a dose of 0.01 mg/kg haloperidol, which significantly enhanced CR responding ($p < 0.01$), and a dose of 0.25 mg/kg, which significantly attenuated CR responding ($p < 0.05$). NCR responding was also significantly increased following administration of a dose of 0.01 mg/kg of haloperidol ($p < 0.01$).

SCH23390

The effect of treatment with the D_1 receptor antagonist SCH23390 can be seen in Figure 6. A one-way ANOVA performed on CR responding revealed a significant effect of drug administration [$F(4, 25) = 3.9, p < 0.05$], and post hoc analysis revealed that this was as a result of treatment with a dose of 0.05 mg/kg, which significantly reduced CR responding ($p < 0.01$). NCR responding was not significantly altered following treatment with any dose of SCH23390.

DISCUSSION

Establishment of conditioned reward in the rat has been shown previously, following pairings of reinforcers with both light (4,11,22,33) and tone (7) stimuli. Results from the present studies indicate that pairing of the compound CS with the delivery of a food pellet resulted in the stimulus acquiring rewarding properties, as indicated by the preference for responding on the lever resulting in presentation of the CS (CR).

d-Amphetamine has previously been shown to enhance responding for a conditioned reinforcer, both when injected peripherally (6,14,25) and when administered directly into the nucleus accumbens (20,33,37), and similar results have been

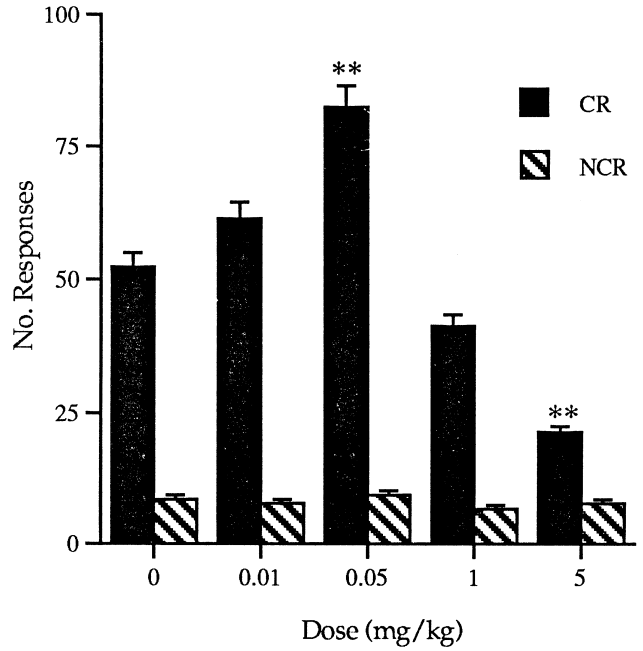

FIG. 4. Effect of raclopride (0.01–5 mg/kg IP, 30 min prior to testing) on responding for a conditioned reinforcer (n = 6 subjects per group). Data are shown as mean ± SEM square root of responses on CR (conditioned reinforcement lever) and NCR (nonconditioned reinforcement lever) over a 30 min test period. Significant effect of drug compared with vehicle treatment: $**p < 0.01$ (Dunnett's t-test).

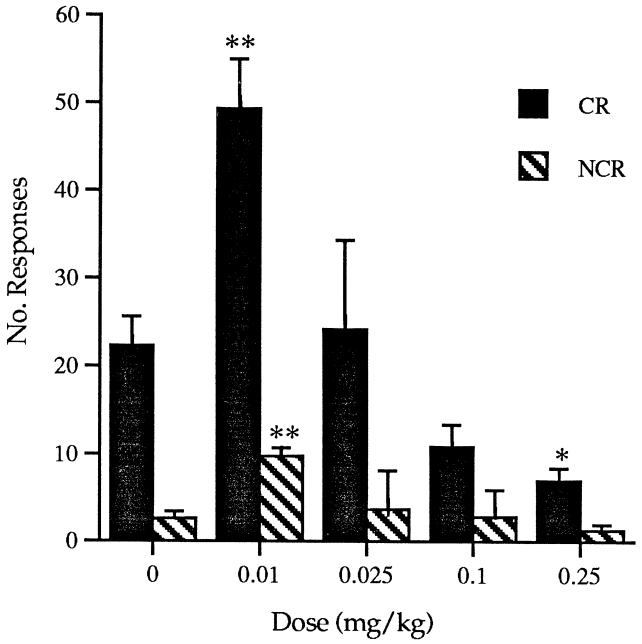

FIG. 5. Effect of haloperidol (0.01–0.25 mg/kg IP, 30 min prior to testing) on responding for a conditioned reinforcer (n = 6 subjects per group). Data are shown as mean ± SEM square root of responses on CR (conditioned reinforcement lever) and NCR (nonconditioned reinforcement lever) over a 30 min test period. Significant effect of drug compared with vehicle treatment on CR responding: $*p < 0.05$, $**p < 0.01$; and NCR responding: $††p < 0.01$ (Dunnett's t-test).

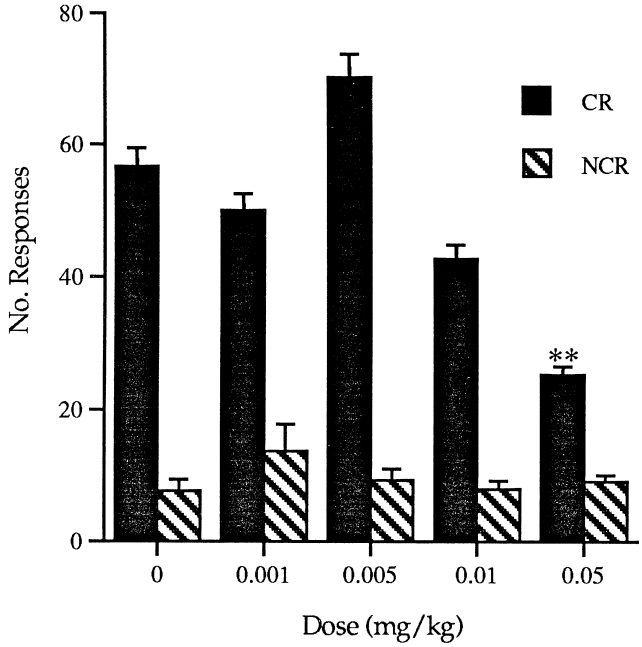

FIG. 6. Effect of SCH23390 (0.001–0.05 mg/kg SC, 120 min prior to testing) on responding for a conditioned reinforcer (n = 6 subjects per group). Data are shown as mean ± SEM square root of responses on CR (conditioned reinforcement lever) and NCR (nonconditioned reinforcement lever) over a 30 min test period. Significant effect of drug compared with vehicle treatment: $**p < 0.01$ (Dunnett's t-test).

obtained following peripheral administration of other psychomotor stimulants, including cocaine (18) and pipradol (3,4,23,25). In agreement with these findings, the present studies showed that relatively low doses of *d*-amphetamine increased CR responding. Higher doses of *d*-amphetamine (0.75–1.0 mg/kg), however, decreased responding on both CR and NCR. The attenuation of responding on the control lever (NCR) indicates that amphetamine treatment leads to a nonspecific reduction in operant activity, rather than an attenuation of the motivational properties of the CS. Previous research has indicated variations in the doses of amphetamine reported to reduce responding on CR and NCR (6,14,25), and care needs to be taken in considering the strain and sex of the animals used when comparing data.

Low doses of the selective D_2 receptor antagonists sulpiride, pimozide, and raclopride significantly increased responding for a conditioned reinforcer, similar to that observed following *d*-amphetamine treatment. In contrast, low doses of the D_1 receptor antagonist SCH23390 failed to affect CR responding, although administration of a dose of 0.005 mg/kg did cause a trend towards an increase in responding on CR. In addition, low doses of the nonselective DA receptor antagonist haloperidol increased responding on both CR and NCR. Selective potentiation of CR responding observed following treatment with low doses of sulpiride, pimozide, and raclopride, but not SCH23390 or haloperidol, complements previous studies showing that D_2 selective receptor antagonists can enhance incentive motivation. Guyon and colleagues (10) observed potentiated food-induced conditioned place preference (CPP) following treatment with the D_2 receptor antagonists sulpiride and pimozide at doses similar to those used in the present study. In that study, low doses of D_2 antagonists enhanced the acquisition of food-induced CPP, thus the antagonists were administered during the conditioning phase of the experiment. It was concluded that antagonism at D_2 receptors enhanced the incentive properties of the primary reinforcer, food. In contrast, in the present study, the compounds were administered following conditioning, i.e., during the testing phase only, therefore antagonism at D_2 receptors enhanced the reinforcing properties of a conditioned or secondary reinforcer. However, Guyon and colleagues (10) observed no effect with higher doses of SCH23390 or with low doses of haloperidol. These discrepancies may indicate differences between the acquisition and expression of the secondary reinforcing properties of food.

Sulpiride, raclopride, and pimozide are highly selective dopamine D_2 receptor antagonists, and it may therefore be suggested that their effects in the present study may be mediated by D_2 receptors (16,29,30). Some dopaminergic neurones have presynaptic autoreceptors on their dendrites and soma. These autoreceptors are of the D_2 subtype (34,35), and it has been suggested that blockade of D_2 autoreceptors may result in a reduction of the inhibitory control over DA release and thus an increase in the amount of DA available within the synaptic cleft (29,31). DA release is increased in the nucleus accumbens when an animal is presented with rewarding stimuli; this strongly suggests that there is a DA involvement in incentive motivation (19). Therefore, the increased responding on treatment with D_2 receptor antagonists could be as a consequence of D_2 autoreceptor blockade leading to an enhancement of the increase in DA neurotransmission within the nucleus accumbens induced by presentation of the CS, which would provide behavioural effects similar to those induced by

DA agonists (2). Haloperidol also led to an increase in responding for a conditioned reinforcer at low doses; however, this enhancement was accompanied by an increase in responding on NCR. This nonselective increase in responding indicates that haloperidol has nonspecific stimulant effects; thus, the CS no longer controls responding.

Higher doses of the D_2 receptor antagonists sulpiride, pimozide, and raclopride, the nonselective DA receptor antagonist haloperidol, and the D_1 receptor antagonist SCH23390 failed to potentiate responding for conditioned reinforcement; in contrast, and in agreement with previous studies, they acted to reduce responding (11,37). Both SCH23390 and raclopride have been shown to inhibit the potentiating effects of intra-accumbens *d*-amphetamine on responding for conditioned reinforcement (37), and SCH23390 has been shown to attenuate bromocriptine-enhanced responding for a conditioned reward (22). Reductions in operant responding for food (15,17,27,28) occur following treatment with both D_1 and D_2 antagonists, which would suggest that both receptor subtypes may be involved in the mediation of food reinforcement (16). Thus, the DA receptor antagonists with selectivity for both D_1 and D_2 receptors used in the present study, at doses likely to block postsynaptic DA receptors, reduced conditioned reward.

In summary, present and previous studies (5,11,37) show that treatment with higher doses of both D_1 and D_2 receptor antagonists, as well as a nonselective D_1/D_2 receptor antagonist, can attenuate operant responding for a conditioned reinforcer. These data indicate that both D_1 and D_2 receptor subtypes are involved in reducing incentive motivation. However, most importantly, findings of the present study show that dopamine receptor antagonists can increase incentive motivation. Thus, results showed that responding for a conditioned reward was selectively potentiated following administration of low doses of D_2, but not D_1/D_2 or D_1, receptor antagonists. Thus, it may be that antagonism at D_2 receptors can enhance the motivational properties of a conditioned reinforcer. Further studies are needed to determine the mechanism by which this effect is mediated.

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