

Effects of extinction, pimozide, SCH 23390, and metoclopramide on food-rewarded operant responding of rats

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Abstract. The similarity in the pattern of responding produced by extinction and dopamine (DA) receptor blockers has led to the suggestion that DA neurons may participate in the usual effects of reward on behaviour. The purpose of the present study was to evaluate the effect of receptor-subtype specific DA antagonists on food-rewarded operant responding. Rats were trained to lever press for food on a variable interval 30-s schedule. They then received one of the following treatments prior to testing on the next 5 days: saline, nonreinforcement, the DA receptor blocker pimozide (0.5 or 1.0 mg/kg), the D1 receptor blocker SCH 23390 (0.01, 0.05, 0.1 mg/kg), and the D2 receptor blocker metoclopramide (1.0, 5.0, 10.0 mg/kg). Nonreinforcement resulted in both intra- and intersession declines in responding. The drugs produced dose-dependent decreases in overall responding. Additionally, both doses of pimozide and the higher doses of SCH 23390 and metoclopramide altered intrasession patterns of responding when compared to saline, with their greatest effect being in the latter portion of the session. Intersession declines were seen with the highest doses of SCH 23390 and metoclopramide and control studies showed that these declines could not be attributed to a buildup of the drug with repeated dosing. It was concluded that both D1 and D2 receptors participate in the control of behaviour by reward.

Key words: Extinction – Pimozide – SCH 23390 – Metoclopramide – Reward – Dopamine – D1 receptors – D2 receptors – Variable interval schedule – Rats

“The term ‘extinction’ is used interchangeably for operation and result” (Mackintosh 1974, p 405). The operation is the omission of reward and the result is a cessation of responding, a gradual decline over time observable both within a daily session and across sessions from day to day (Skinner 1938). Wise et al. (1978) were the first to report that pimozide, a dopamine (DA) receptor blocker, produced a pattern of responding that resembled extinction and concluded that the two operations were equivalent. However, a large number of subsequent studies showing this not to be the case (e.g., Phillips and Fibiger 1979) led to the conclusion that treatment with DA receptor blockers produces motoric impairments. This conclusion is in good agreement with an extensive literature reporting that de-

creased DA neurotransmission leads to hypokinesia and catalepsy (Ungerstedt 1979).

Although pimozide-produced decreases in operant responding are not *equivalent* to extinction, the pattern is strikingly *similar* to the typical extinction curve. Animals treated with DA receptor blockers show intra- and intersession declines in responding (Tombaugh et al. 1980). These results cannot be attributed to simple motoric effects which would be expected to remain constant over days. Thus, the effect of DA receptor blockers on intermittently rewarded responding can provide evidence for the role of DA in reward if the intrasession and intersession time course of the drug effect is charted.

The present experiments used this approach to evaluate the effects of several DA receptor blockers. DA receptors have been found to be of at least two types: D1 are linked to and stimulate the enzyme, adenylate cyclase whereas D2 do not (Kebabian and Calne 1979). The purpose of the present study was to compare the effects of drugs known to act specifically at each DA receptor subtype to evaluate their relative contribution to the role of DA in reward. D1 receptors were blocked with the drug [R-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepine-7-ol] (SCH 23390). This compound has been shown to potentially antagonize the ability of DA to stimulate adenylate cyclase and to antagonize [³H]-piflutixol binding to D1 receptors while only weakly inhibiting the binding of [³H]-spiperone or [³H]-haloperidol to D2 receptors. The distribution of [³H]-SCH 23390 binding sites in rat brain has been shown to be well correlated with levels of endogenous DA. Furthermore, SCH 23390 only weakly affects serotonergic and adrenergic receptors while being devoid of anticholinergic and antihistaminergic effects (Cross et al. 1983; Hyttel 1983; Iorio et al. 1983; Schulz et al. 1985). D2 receptors were blocked with the drug metoclopramide. This compound is without effect on the ability of DA to stimulate adenylate cyclase from rat striatum but strongly displaces the binding of [³H]-haloperidol or [³H]-spiperone at D2 receptors and stimulates the release of prolactin, a classic D2 receptor-mediated effect. Metoclopramide increases homovanillic acid levels in the brain, an index of the blockade of DA receptors, but has little effect on the metabolites of noradrenalin or serotonin (Jenner et al. 1975, 1978; Peringer et al. 1976; Elliott et al. 1977; Harrington et al. 1983). Finally, pimozide was used as a reference DA receptor blocker that antagonizes both D1 and D2 receptors (Creese 1983).

Methods

Subjects. Experimentally naive male rats of the Wistar strain, obtained from Charles River Canada, Inc., weighed 200–300 g at the beginning of the experiment. All rats were housed individually in a climatically controlled ($21 \pm 1^\circ \text{C}$) colony room kept on a 12 h light (0600–1800 hours)/dark cycle and were maintained at 80% of their free-feeding weights by daily feeding with measured rations. Water was always available in the home cage.

Apparatus. Four similar behavioral testing chambers ($23.0 \times 20.4 \times 19.5 \text{ cm}$) each consisted of aluminum plate sides with clear Plexiglas top and doors. The floor was composed of aluminum rods spaced 1.5 cm apart. A lever (5.0 cm wide) was located on the right wall at a height of 5.5 cm and a feeder cup was positioned to the right of the lever. The chamber was illuminated by a light and enclosed in an outer wooden box insulated with sound attenuating Styrofoam and ventilated by a small fan. Data collection and schedule of reinforcement were controlled by a Digital Equipment Corporation LSI 11/2 computer.

Procedure. All rats were conditioned to press the lever for food pellet reinforcers (45 mg Bioserv Dustless Precision Pellets) and given several 30-min sessions of continuous reinforcement followed by a session in which reinforcers became available every 15 s on the average, a variable interval (VI) 15-s schedule. On each of the following 10 experimental days at approximately the same time each day, 5 days a week, each rat received a 30-min session with reinforcers presented according to a VI 30-s schedule. Days 9 and 10 were defined as the baseline days and only rats achieving baseline response rates (responses per min) greater than or equal to 10 and less than or equal to 50 were included in subsequent test sessions. A total of 112 rats were included and another 27 failed to reach criterion baseline rates and never received drugs.

Trained rats were randomly assigned to the following groups: saline ($n=8$), nonreinforcement ($n=6$), pimozide doses of 0.5 ($n=5$) or 1.0 mg/kg ($n=12$), SCH 23390 doses of 0.01 ($n=8$), 0.05 ($n=7$) or 0.10 mg/kg ($n=8$) and metoclopramide doses of 1.0 ($n=7$), 5.0 ($n=9$) or 10.0 mg/kg ($n=7$). Nonreinforcement animals received five 30-min sessions of testing in extinction. Animals in all drug groups continued to receive food according to the VI 30-s schedule each day for the five 30-min test sessions and each session was preceded with injection of the appropriate dose and drug.

Rats receiving the highest doses of SCH 23390 (0.1 mg/kg) and metoclopramide (10.0 mg/kg) showed extinction-like decreases in responding over days. One possibility is that the drug was not completely cleared from the body 24 h following injection. To evaluate this possibility, rats were conditioned and trained to baseline as described above. One each of the next 3 days one group ($n=10$) received injections of SCH 23390 (0.1 mg/kg) and the other ($n=9$) its vehicle, a third group ($n=8$) received injections of metoclopramide (10.0 mg/kg) and another ($n=8$), saline and were returned to their home cages. Testing took place on the next 5 days. Prior to each session those rats pretreated with SCH 23390 and its vehicle were injected with SCH 23390 (0.1 mg/kg) and the other two groups received metoclopramide (10.0 mg/kg). If the observed extinction-

like decline in responding was a consequence of a build-up of the drug, the drug-pretreated groups would be expected to respond at lower rates than the vehicle pretreated groups.

Drugs. Pimozide (Janssen Pharmaceutica) was dissolved in boiling tartaric acid (6.0 mg/ml) and cooled to room temperature prior to injection. IP injections (1.0 ml/kg) preceded behavioural testing by 4.0 h. SCH 23390 (Schering Corp.) was suspended in a small quantity of the polymer, polyoxyethylene sorbitan mono-oleate (Tween 80) and added to distilled water to an appropriate concentration to yield an injection volume of 1.0 ml/kg. SCH 23390 was injected SC 2.0 h prior to testing. Metoclopramide hydrochloride (Laboratoires Nordic Inc.) was dissolved in distilled water and injected IP (1.0 ml/kg) 2.0 h prior to testing.

Data analyses. Response rates (responses per min) were analyzed using analysis of variance. Whenever repeated measures were included in the analyses, the Greenhouse and Geisser (see Keppel 1973) adjusted degrees of freedom were used to reduce positive bias in F values resulting from violations of homogeneity assumptions. The P values based on these adjusted degrees of freedom were provided by the BMDP4V Statistical Software package.

Results

For all groups, only the baseline (days 9 and 10 of training and test days will be considered. Figure 1A shows responses per min for each 5-min segment of each 30-min session for the saline and nonreinforcement groups. Both groups showed intrasession increases during baseline. The saline group continued to show this pattern of responding during each of the test days as well as a tendency to respond at higher rates from day to day. The small differences in response rate between the two groups during baseline presumably were due to sampling error. The nonreinforcement group showed a clear extinction effect over test days, rates decreasing both within and across sessions. Analysis of variance (ANOVA) comparing baseline rates of the two groups at six time intervals yielded no significant main effect of group or day or any interactions, but, as expected, the time effect was significant [$F(2.3,27.0)=8.01$, $P<0.001$]. An ANOVA comparing groups on test days yielded main effects of group [$F(1,12)=22.75$, $P<0.001$] and interaction of group by day [$F(1.5,18.2)=6.34$, $P<0.01$] and group by time [$F(1.6,19.5)=13.78$, $P<0.001$]. These interaction suggest that the groups differed in response rate over days and across time. Separate within-group ANOVAs of response rates during test sessions confirmed this. The saline group showed significant increases over time [$F(1.5,10.3)=9.31$, $P<0.01$] with no significant day effect, whereas the nonreinforcement group showed decreases in response rate over time [$F(2.2,11.2)=9.81$, $P<0.01$] and across days [$F(2.1,10.4)=17.54$, $P<0.001$]. The results of the analyses confirm that the VI 30-s schedule maintains stable response rates that show typical extinction when reward is no longer presented.

Results for the pimozide groups are shown in Fig. 1B. The groups appeared to differ little in baseline rates. During testing, both doses resulted in a flattening of intrasession response rates. The dose of 0.5 mg/kg resulted in a gradual decline in response rates over days whereas the higher dose, although reducing rates, did not appear to result in systematic

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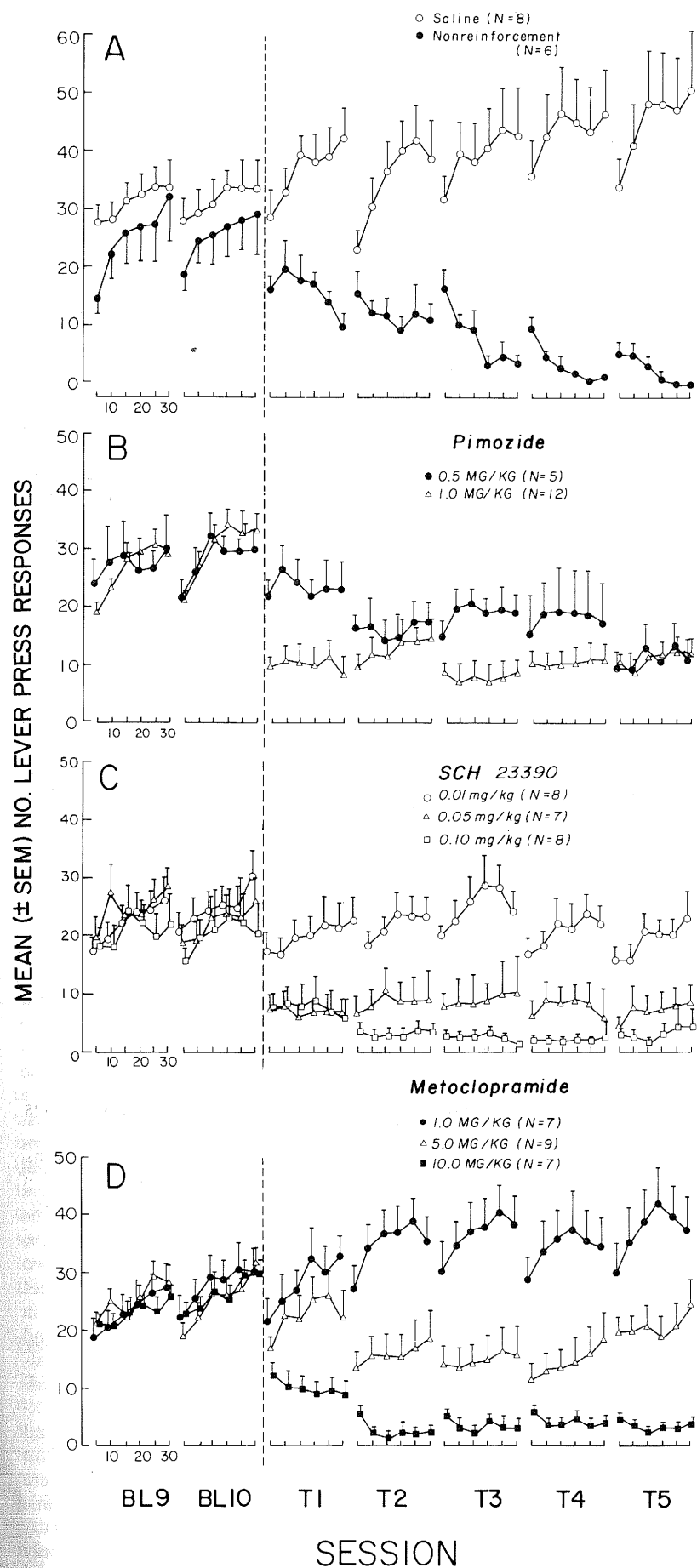


Fig. 1A-D. Mean ($\pm$ SEM) responses per min for each 5-min segment of the two 30-min baseline days (BL9 and BL10) and the 5 test days (T1-T5) for the saline and nonreinforcement groups (A), groups receiving 0.5 or 1.0 mg/kg pimozide during the test (B), groups receiving 0.01, 0.05 or 0.10 mg/kg SCH 23390 during the test (C), and groups receiving 1.0, 5.0 or 10.0 mg/kg metoclopramide during the test (D).

A $\circ$ Saline ($n=8$), $\bullet$ Nonreinforcement ($n=6$);
B Pimozide: $\bullet$ 0.5 mg/kg ($n=5$), Δ 1.0 mg/kg ($n=12$);

C SCH 23390: $\circ$ 0.01 mg/kg ($n=8$), Δ 0.05 mg/kg ($n=7$), $\square$ 0.10 mg/kg ($n=8$);

D Metoclopramide: $\bullet$ 1.0 mg/kg ($n=7$), Δ 5.0 mg/kg ($n=9$), $\blacksquare$ 10.0 mg/kg ($n=7$)

atic decreases over days. An ANOVA comparing baseline rates of the saline and two pimozide groups yielded no significant main effects or interactions except a main effect of time [$F(3.4,73.9)=16.23$, $P<0.001$]. An ANOVA comparing the three groups on test days yielded main effects of group [$F(2,22)=22.12$, $P<0.001$] and time [$F(1.8,39.0)=10.20$, $P<0.001$] as well as a significant interaction of these two variables [$F(3.6,39.0)=6.60$, $P<0.001$]. Subsequently, ANOVAs making pairwise comparisons showed that the 0.5 mg/kg [$F(1,11)=9.24$, $P<0.01$] and the 1.0 mg/kg groups [$F(1,18)=37.49$, $P<0.001$] differed from saline and from each other [$F(1,15)=6.69$, $P<0.05$]. The time-by-group interaction was significant in the comparison of each drug group with saline [$F(1.6,18.1)=4.07$, $P<0.05$ and $F(1.6,29.2)=10.36$, $P<0.001$] but not to each other [$F(3.0,45.0)=1.00$, $P>0.05$]. This suggests that the interaction occurred as a result of the flattening across time of intrasession response rates compared to the consistent intrasession increases seen in the saline group. Although the 0.5 mg/kg group appeared to show a day-to-day decline in response rates, there was no significant interaction of day and group in the overall ANOVA [$F(5.2,57.3)=1.72$, $P>0.05$].

Results for the SCH 23390 groups are shown in Fig. 1C. Again the groups appeared to differ little in baseline rates. During testing, there was a dose-dependent decrease in overall responding. It also appeared that intrasession rates were progressively more flattened with increasing dose. Finally, the 0.10 mg/kg dose appeared to result in a stepwise decline in rates, especially over the first 2 test days. An ANOVA comparing baseline rates of the saline and SCH 23390 groups revealed only a significant effect of time [$F(5,135)=13.51$, $P<0.001$]. An ANOVA comparing the four groups on test days yielded main effects of group [$F(3,27)=21.28$, $P<0.001$], time [$F(1.7,45.5)=11.93$, $P<0.001$] and an interaction of these two variables [$F(5.1,45.4)=4.76$, $P<0.001$]. ANOVAs comparing each dose to saline showed a significant difference in each case [$F(1,14)=9.25$, $P<0.01$; $F(1,13)=22.96$, $P<0.001$; $F(1,14)=40.31$, $P<0.001$ for 0.01, 0.05, and 0.10 mg/kg, respectively]. The 0.01 mg/kg group differed from the 0.05 [$F(1,13)=10.44$, $P<0.01$] and 0.10 mg/kg doses [$F(1,14)=35.80$, $P<0.001$], the latter two not differing significantly from one another [$F(1,13)=1.55$, $P>0.05$]. The time-by-group interaction was significant in the comparison of the 0.05 and 0.10 mg/kg groups to saline [$F(1.7,21.5)=5.51$, $P<0.05$; $F(1.5,21.1)=8.92$, $P<0.01$, respectively] and for the comparison of 0.01 to 0.10 mg/kg [$F(1.6,22.0)=4.00$, $P<0.05$] but not for the comparison of saline to 0.01 mg/kg [$F(1.5,21.4)=2.93$, $P>0.05$], 0.01 to 0.05 mg/kg [$F(1.8,23.9)=2.13$, $P>0.05$] or 0.05 to 0.10 mg/kg [$F(1.8,23.7)<1$, $P>0.05$]. These results confirm that the within-session increases in response rates seen in the saline group were progressively more attenuated with increasing doses of SCH 23390. As was the case with pimozide, there was no significant interaction of group and day in the overall ANOVA [$F(5.6,50.0)=2.00$, $P>0.05$]. Thus, the apparent decline in response rates from test day 1 to 2 of the group receiving 0.10 mg/kg SCH 23390 was not significant.

Results for the metoclopramide groups are shown in Fig. 1D. The groups differed little in baseline rates. During testing, there was a dose-dependent decrease in overall responding. For the 10.0 mg/kg group, intrasession rates seemed to be flattened and for both the 5.0 and 10.0 mg/kg

groups, rates appeared to decrease from test day 1 to 2. An ANOVA comparing baseline rates of the saline and metoclopramide groups revealed a significant effect of time [$F(3.2,86.3)=20.56$, $P<0.001$] but groups did not differ significantly. An ANOVA comparing the four groups on test days yielded main effects of group [$F(3,27)=16.11$, $P<0.001$] and time [$F(1.7,46.3)=16.34$, $P<0.001$], a time-by-group interaction [$F(5.2,46.3)=5.08$, $P<0.001$] and a day-by-group interaction [$F(6.0,53.6)=2.61$, $P<0.05$]. ANOVAs comparing each dose to saline showed a reliable difference for 5.0 [$F(1,15)=12.64$, $P<0.01$] and 10.0 [$F(1,13)=33.86$, $P<0.001$] but not for 1.0 mg/kg [$F(1,13)<1.0$, $P>0.05$]. The 1.0 and 5.0 mg/kg doses differed from each other [$F(1,14)=10.57$, $P<0.01$] and both differed from the 10.0 mg/kg dose [$F(1,12)=52.65$, $P<0.001$ and $F(1,14)=11.86$, $P<0.01$]. The time-by-group interaction was significant in the comparison of 5.0 and 10.0 mg/kg with saline [$F(1.5,21.7)=4.00$, $P<0.05$ and $F(1.5,19.7)=10.52$, $P<0.01$] and for the comparison of 1.0 with 10.0 mg/kg [$F(2.5,30.2)=12.86$, $P<0.001$]. These results show that the intrasession increases in response rate seen in the saline group were progressively more attenuated by higher doses of metoclopramide. A day effect was observed when the 5.0 and 10.0 mg/kg doses were combined [$F(2.1,29.6)=6.43$, $P<0.01$] and a day-by-group interaction was seen in the comparison of the 1.0 and 10.0 mg/kg groups [$F(2.9,34.2)=5.49$, $P<0.01$]. Finally, day effects were observed separately in the 5.0 [$F(2.0,15.8)=3.88$, $P<0.05$] and 10.0 mg/kg groups [$F(1.6,9.9)=5.40$, $P<0.05$]. Thus, metoclopramide produced a dose-dependent decrease in operant responding. Furthermore, the higher doses produced a reliable extinction-like intersession decline in responding and the 10.0 mg/kg dose produced an intrasession extinction-like decrease in responding.

One possible explanation for the effects of 10.0 mg/kg metoclopramide is that this high dose accumulated in the body, resulting in an increase in the drug level with each repeated dose. The pretreatment groups were included to test this possibility. Although the high dose of SCH 23390 did not produce a reliable day-to-day decline in responding, there appeared to be a decrease in responding from test day 1 to 2. Therefore, pretreatment groups also were tested with this drug. Results for SCH 23390 are shown in Fig. 2A. There appeared to be little difference between the groups during baseline. In test sessions the groups were similar, both showing declining response rates over days. An ANOVA comparing baseline rates of the two groups revealed only a significant time effect [$F(2.3,39.7)=8.93$, $P<0.001$]. An ANOVA comparing the groups on test days revealed that response rates declined significantly over time [$F(2.1,36.2)=46.8$, $P<0.01$] and across days [$F(3.0,51.2)=12.61$, $P<0.001$] and there was an interaction of these two variables [$F(6.7,113.9)=2.41$, $P<0.05$]. The groups did not differ significantly and each showed a reliable decrease in rate over days [$F(2.1,17.0)=6.63$, $P<0.01$ and $F(3.33,24.6)=7.97$, $P<0.001$]. Thus, home cage pretreatment appeared to have little significant effect on the decline in responding seen during testing with SCH 23390.

Results for the metoclopramide pretreatment group and its control are shown in Fig. 2B. The groups appeared to be similar during baseline. During testing they also were similar, showing an intrasession and intersession decline in responding, especially over the first 2 days. An ANOVA comparing baseline rates of the two groups revealed only

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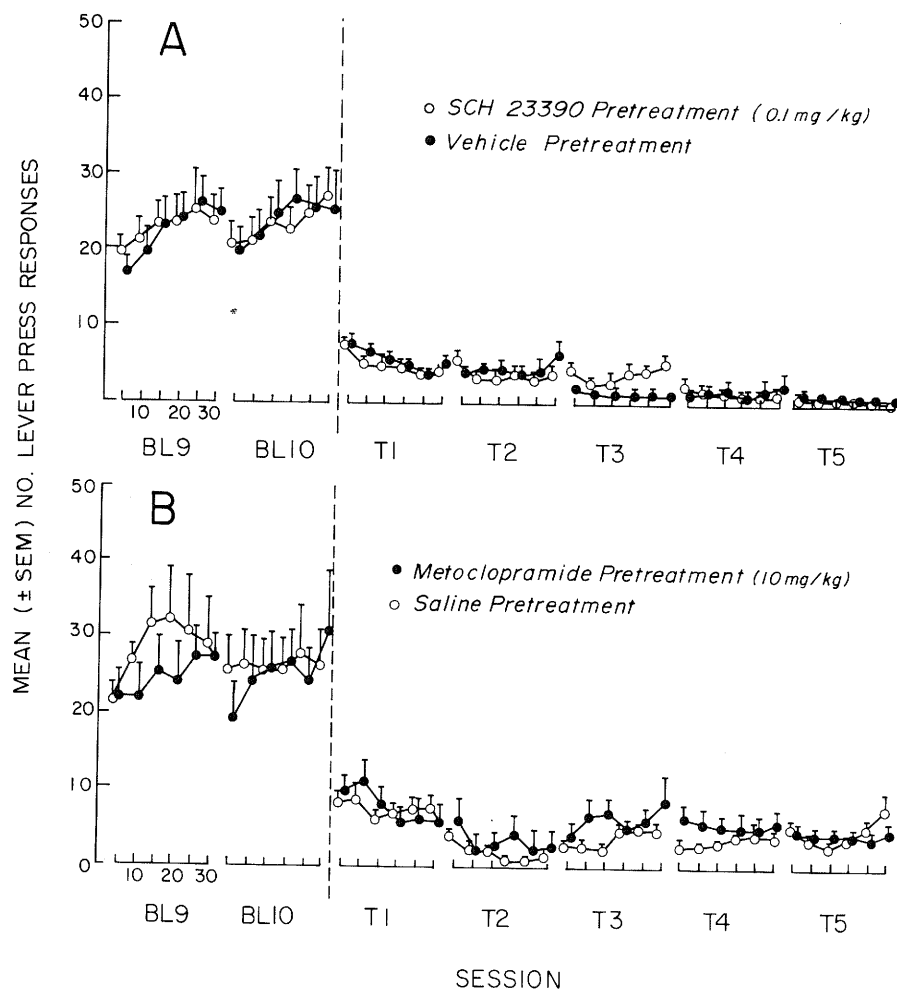


Fig. 2A, B. Mean ($\pm$ SEM) responses per min for each 5-min segment of the two 30-min baseline days (BL9 and BL10) and the 5 test days (T1–T5) for groups receiving pretreatment with 0.10 mg/kg SCH 23390 ($n=10$) or its vehicle ($n=9$) for 3 days prior to testing with 0.10 mg/kg SCH 23390 (A), and for groups receiving pretreatment with 10.0 mg/kg metoclopramide ($n=8$) or saline ($n=8$) for 3 days prior to testing with 10.0 mg/kg metoclopramide (B). A ○ SCH 23390 pretreatment (0.1 mg/kg), ● Vehicle pretreatment; B ● Metoclopramide pretreatment (10 mg/kg), ○ Saline pretreatment

a time effect [$F(2.2,31.0)=4.11$, $P<0.05$]. An ANOVA comparing the groups on test days revealed that they did not differ significantly from one another. Response rates decreased over days [$F(2.8,39.4)=15.28$, $P<0.001$] and there was a day-by-time interaction [$F(6.4,90.0)=4.49$, $P<0.001$]. The interaction occurred because response rates tended to decrease over time during the first and second test sessions and then tended to increase slightly or remain fairly constant over time in the last three test sessions.

Discussion

The observation that DA receptor blocking drugs produced decreases in responding is in good agreement with an extensive literature reporting that treatment with these agents leads to decreased motor activity (Ungerstedt 1979). However, the significant time by group interactions seen in comparisons of each pimozide dose with saline suggest that pimozide also produced a relative decline in intrasession response rates, an observation consistent with a role for

DA in the control of behaviour by reward. It is noteworthy, however, that pimozide did not produce intrasession declines like those seen in extinction. Similar effects have been reported following treatment with pimozide (Beninger 1982) or haloperidol (Salamone 1986). Pimozide has also been reported to produce day to day declines in intermittently rewarded responding (Gray and Wise 1980). Although not significant in the present study, perhaps as a result of the small sample size ($n=5$), the 0.5 mg/kg pimozide dose appeared to produce a similar day-to-day decline.

Both SCH 23390 and metoclopramide produced dose-dependent intrasession flattening of response rates as evidenced by significant time by group interactions in comparisons of the higher doses with saline. Again, however, intrasession declines like those seen in extinction were not observed. Metoclopramide also produced a significant day-to-day decline in responding. The highest dose of SCH 23390 appeared to similarly result in a decrease in response rates from test session 1 to 2. Although this effect was not significant in the analyses comparing doses of SCH 23390 and

saline, a significant decrease was observed in the pretreatment experiment when only groups treated with 0.10 mg/kg were considered. These findings, like those with pimozide, are consistent with the hypothesis that DA plays a role in the control of behaviour by reward.

One possibility is that day-to-day declines in responding in animals treated with DA receptor blockers result from incomplete clearing of the drug from the body over 24 h. When the next injection occurs, this putative drug residual may increase the dose leading to a larger decline in responding than seen on the previous day. Pretreatment groups given three home cage injections of SCH 23390 or metoclopramide prior to testing with these drugs did not differ significantly from nonpretreated controls. Thus, day-to-day declines in responding cannot be attributed to drug accumulation, a finding in accordance with similar studies done with pimozide (Mason et al. 1980; Beninger et al. 1983).

Previous studies have shown that both D1 and D2 receptors participate in the control of locomotor behaviour by DA. Thus, locomotor activity was increased by D1 (Setler et al. 1978) and D2 agonists (Beninger et al. 1985) and decreased by D1 (Hoffman and Beninger 1985) and D2 antagonists (Elliott et al. 1977). Previous studies also have shown that both D1 and D2 receptors participate in the control of the behavioural effects of reward by DA. Woolverton et al. (1984), investigating intravenous self-administration of DA agonists by rhesus monkeys, recently reported that only D2 agonists were effective rewards for maintaining this behaviour. Based on a high correlation between the ability of drugs to produce extinction of medial forebrain bundle self-stimulation and their affinity for D2 receptors, Gallistel and Davis (1983) similarly concluded that D2 receptors are critically involved in brain stimulation reward. On the other hand, Nakajima and McKenzie (1986) recently reported that SCH 23390 produced a within-session decline in responding for brain stimulation reward, a result in agreement with the present findings and supportive of a role for D1 receptors in the control of behaviour by reward. A similar conclusion was drawn by Ferrer et al. (1983), who compared the effects of intrafrontal cortex injections of various drugs affecting DA receptors on electrical self stimulation in the frontal cortex ipsilateral or contralateral to the injection site and deduced that D1 receptors were critically involved in reward in this area. These and the results of the present study suggest that both D1 and D2 receptors may participate in the control of behaviour by reward. Thus, both SCH 23390 and metoclopramide at higher doses produced a pattern of responding somewhat similar to that seen in extinction. The precise nature of the contribution of DA receptor subtypes to the control of behaviour by reward awaits further study.

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