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Effects of Dopamine Antagonists and Accumbens Dopamine Depletions on Time-Constrained Progressive-Ratio Performance

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ABERMAN, J. E., S. J. WARD AND J. D. SALAMONE. *Effects of dopamine antagonists and accumbens dopamine depletions on time-constrained progressive-ratio performance.* PHARMACOL BIOCHEM BEHAV **61**(4) 341–348, 1998.—Four experiments were conducted to determine the effects of dopamine (DA) antagonists and DA depletions on progressive-ratio responding for food reinforcement. On this schedule, ratio requirement increased by one response after each reinforcer was obtained, and rats were tested in 30-min sessions. Response rates and highest ratio completed were reduced in a dose-related manner by systemic injections of the D_1 antagonist SCH 23390, and also by the D_2 antagonists haloperidol and raclopride. Drug-treated rats also showed reductions in time to complete the last ratio, demonstrating that they had stopped responding before the end of the session. DA depletions produced by injections of 6-OHDA directly into the nucleus accumbens substantially decreased both the number of responses and the highest ratio completed. The deficits in response number and highest ratio completed induced by DA depletions persisted through the first 3 weeks of postsurgical testing, with some recovery by the fourth week. However, the deficits resulting from dopamine depletions were largely a manifestation of a decrease in response rate; although time to complete the last ratio was significantly reduced by dopamine depletions in the first few days of testing, rats recovered on this measure by the fifth day after surgery. Although previous work has shown that performance on several schedules (e.g., continuous, low value ratios, variable interval) is relatively unaffected by accumbens DA depletions, the present data demonstrate that such depletions do produce a substantial and persistent impairment of progressive ratio response output. Rats with accumbens DA depletions appear to have deficits in maintaining the high work output necessary for responding at large ratio values. The relative sparing of responding on some simple schedules, together with the present progressive ratio results, suggest that rats with accumbens DA depletions remain directed toward the acquisition and consumption of food, but they show deficits in work output for food. © 1998 Elsevier Science Inc.

Reward Reinforcement Operant Motivation Progressive ratio Movement Behavioral economics

DOPAMINE (DA) antagonists with various profiles, including pimozide, haloperidol, raclopride, SCH23390, and clozapine, have been shown to suppress instrumental lever pressing for food reinforcement (3,39,40,45,60). Recently, considerable attention has been focused the role of accumbens DA in instrumental behavior. It has been suggested that DA in nucleus accumbens mediates the positive reinforcing effects of stimuli such as drugs of abuse (5), as well as natural reinforcers such as food (16,51). However, there is considerable evidence against the idea that accumbens DA mediates the primary reinforcing or motivating characteristics of stimuli such as food. Several reports have demonstrated that fundamental aspects of food motivation, such as food consumption, are left intact after accumbens DA depletions or injections of haloperidol into the accumbens (2,25,48). Responding on a continuous reinforcement (CRF) schedule is generally thought to be highly dependent upon food motivation [e.g., (49)], yet this schedule is relatively insensitive to the effects of accumbens DA depletions (29,47). CRF responding is only marginally affected by accumbens DA depletions within the first few days after surgery, and the response patterns that are shown (i.e., initial slowing, relative lack of high rate responses) differ substantially from the effects of extinction (29,47). Responding on a variable-interval 30-s schedule was not reduced by 90% depletions of either the core or shell region of the nucleus accumbens (52). Several years ago, it was demonstrated that accumbens DA depletions that substantially altered cocaine-reinforced responding had little effect upon food-reinforced

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variable ratio 2.5 responding (37). More recently, Caine and Koob (6) employed a multiple-schedule procedure, and demonstrated that accumbens DA depletions did not affect the food-reinforced component, although they did dramatically reduce responding in the cocaine-reinforced component. Direct comparisons of the effects of DA depletions in nucleus accumbens and ventrolateral striatum have shown that the striatal depletions produced severe impairments in FR5 and fixed-interval 30-s responding, while accumbens depletions produced small, transient effects (9,46).

It has been suggested that the effects of accumbens DA depletions interact with the work requirement of the instrumental task [(8,10,11,49,52); see reviews, (41–43)]. Thus, it has been noted that FR5 responding, which generally occurs at a high rate, is more greatly affected by accumbens DA depletions than responding on lower rate schedules such as CRF or VI30 (46,52). In addition, experiments that offered explicit choices between responses with different work requirements have shown that accumbens DA depletions alter relative response allocation; DA depleted rats shift away from highly active instrumental responses, such as lever pressing at high rates or barrier climbing, and instead select less effortful responses even if they generate a lower reinforcement value (8,10,11,43,49). These data have been interpreted to mean that rats with accumbens DA depletions remain directed toward the acquisition and consumption of food, yet they are more sensitive to work-related response costs (41,43,49).

One way of directly assessing the effects of work-related response costs is the progressive-ratio (PR) schedule. With this schedule, the ratio requirement is increased as the animal completes each ratio. Rats typically respond to this incremental ratio requirement by emitting a very large number of responses. In his review of the early PR literature, Stewart (55) suggested that "progressive ratio schedules would be ideal tests of effort expenditure" (p. 19). There are several different types of PR schedules [for review, see (55)], and previous work has involved both open-ended and time-constrained schedules. In open-ended PR schedules, the animal proceeds through an incremental ratio progression, until it reaches the "break point" and stops responding. Although some researchers have assumed that the PR break point is a measure of "reward" [e.g., (7)] or "reward strength" (17), evidence indicates that this measure is affected by several different conditions (31,55,56), including the kinetic requirements of the response (50). Pilot data from our laboratory indicated that, with rats performing on a PR schedule with a 30-min time contraint, very high rates of responding (i.e., 1500–2000 per 30 min) could be achieved. Thus, the present studies were designed to investigate the effects of selective DA antagonists and accumbens DA depletions on PR responding for food reinforcement. A 30-min session time was chosen to ensure high rates of responding, and to be consistent with other studies from our laboratory that used different operant schedules (9,46,47). Previous reports have investigated the effects of selective DA antagonists on instrumental responding under various schedules (3,7,12), but very few studies have examined the effects of DA antagonists or DA-depleting lesions on PR responding for food [e.g., (7)]. The first three experiments examined the effects of systemic administration of the D_1 antagonist SCH 23390 and the D_2 antagonists raclopride and haloperidol on PR lever pressing. In the fourth experiment, the neurotoxic agent 6-hydroxydopamine (6-OHDA) was injected directly into nucleus accumbens to produce a focal depletion of DA. It was hypothesized that, in spite of the literature showing very little effect of accumbens DA depletions on lever pressing on several schedules, the PR schedule should be sensitive to the effects of accumbens DA depletions. In all studies, the rats were trained prior to drug administration or surgery; thus, the present work focused upon the effects of DA-related manipulations on PR performance that was already established by extensive training.

METHOD

Subjects

A total of 36 male Sprague–Dawley rats (Harlan–Sprague–Dawley, Indianapolis, IN) were used for all three experiments. Rats were housed in a colony maintained at 23°C with a 12 L:12 D cycle (lights on at 0700 h). All rats weighed between 315 and 415 g at the beginning of the study. Rats were food deprived to 85% of their free-feeding body weight, but then allowed a modest growth (up to 95% of original weight) over the course of the experiment. Unrestricted access to water was available in the home cages.

Behavioral Procedures

Lever-pressing test sessions were conducted in Med Associates operant chambers (28 × 23 × 23 cm). After magazine training, rats were trained to lever press for 45 mg pellets (Bioserve Inc., Frenchtown, NJ) on a continuous reinforcement schedule (30-min sessions, 5 days per week) for 1 week. Animals were then shifted to the PR schedule. For the present experiments, the PR schedule began with a ratio value of 1, and then the ratio requirement increased by 1 response after each completed ratio. The sessions lasted 30 min, and the computer recorded the total number of responses, the time to complete each ratio, the average interresponse time (IRT) for each ratio, the highest ratio completed, and the time to complete the last ratio. Although a time-constrained PR schedule was used, time to complete the last ratio was used to determine if rats ceased responding (i.e., achieved a "break point") during the session. Training proceeded 5 days a week for 3–4 weeks before any drug treatments or surgeries were conducted.

Drugs

SCH 23390, raclopride, and haloperidol were obtained from Research Biochemicals International (Natick, MA). These drugs were dissolved in a 0.3% tartaric acid vehicle for injection. Sodium pentobarbital (50.0 mg/kg) was used as the anesthesia for surgery.

DA Depletion by Injection of 6-OHDA

Intraaccumbens injections of 6-OHDA were performed with the rats under pentobarbital anesthesia, and all rats received IP injections of 20.0 mg/kg pargyline 30 min prior to surgery. Bilateral injections of 6-OHDA (Research Biochemicals Inc., Natick, MA) were performed via 30-gauge stainless steel injectors directly into the nucleus accumbens (AP + 2.8 mm, ML ± 1.4 mm, DV −7.8 mm; incisor bar 5.0 mm above the interaural line). A total of 12.5 μg of the free base of 6-OHDA dissolved in 1.5 μl of 0.1% ascorbic acid (1.5 μl of 8.33 μg/μl 6-OHDA) was injected per side. Rats in the control groups received 1.5 μl per side of the 0.1% ascorbate solution at the same site as the 6-OHDA–treated rats. The injection was driven at a low flow rate (0.3 μl/min) by a Harvard Apparatus syringe pump; the low flow rate was designed to minimize damage to the local area and reduce spread to more dorsal regions.

Neurochemical Analyses for Tissue Dopamine

After completion of the third experiment, rats were exposed to a carbon dioxide chamber for 30 s, decapitated, and then their brains were quickly removed and frozen. A 16-gauge stainless steel tube was used to dissect tissue samples from 0.75-mm thick coronal sections through the nucleus accumbens and the ventrolateral striatum (VLS). Tissue samples from each region were placed in 200 μl of chilled 0.1 N perchloric acid, homogenized, and centrifuged. The samples tubes were frozen, and the DA content of the supernatant was later analyzed using a high-performance liquid chromatography (HPLC) system that has been described previously (10,11). The mobile phase consisted of a sodium phosphate buffer, with 7.0% methanol, EDTA, and 1.4 ml of a 0.4-mM sodium octyl sulfate solution added as an ion pairing agent to 1 liter of mobile phase. Standards of DA (Sigma Chemical Co.) were assayed before, during, and after the tissue samples.

Experimental Procedures

The first three experiments examined the effects of SCH 23390 ($n = 8$), raclopride ($n = 7$), and haloperidol ($n = 7$) on PR responding. Rats were trained on the PR schedule for a minimum of three weeks (5 days per week, 30-min sessions) prior to any drug testing. After completion of baseline training (all rats exceeded 1200 responses per 30 min by the end of the third week), the drug treatment sessions began. Within each separate drug experiment, there were five drug treatments (tartaric acid vehicle, 0.0375, 0.075, 0.15, and 0.3 mg/kg DA antagonist, all injected IP), and each rat received all five treatments (one injection per week) in a randomly varied order. The 30-min operant test sessions were initiated 60 min after IP injections for SCH 23390, 20 min for raclopride, and 60 min for haloperidol; these times were chosen based upon pilot data. Daily baseline training sessions were continued on those days that were not drug treatment days until the experiment was completed. All rats showed normal levels of responding on the baseline tests conducted between drug sessions.

For the fourth experiment, rats were trained on the PR schedule for at least three weeks (5 days per week, 30-min sessions) prior to surgery. These rats received intracranial injections of either ascorbate vehicle ($n = 7$) or 6-OHDA ($n = 7$) into the nucleus accumbens as described above. Rats were tested on the PR schedule, 5 days per week, for 4 weeks (30-min sessions on days 3–7, 10–14, and 17–21 postsurgery). To maintain body weight, rats received additional lab chow in their home cage. Upon completion of the behavioral testing, rats were decapitated for DA assays as described above.

Statistical Analysis

The first three experiments were repeated-measures designs, because each animal received all drug treatments. Thus, the total number of responses and the break points were analyzed by repeated measures analysis of variance (ANOVA; Systat 5.0). In addition, orthogonal analysis of trend was used to determine the relation between dose and response. The fourth experiment was a 2 group (vehicle vs. 6-OHDA) by 4 week design, with repeated measures on the week factor; this experiment was therefore analyzed with 2×4 factorial ANOVAs with repeated measures (Systat 5.0). Weekly averages for total number of responses and break point were analyzed. Analysis of simple main effects (24) was used to analyze the sources of any interaction effects. In addition, analysis of covariance with baseline responding as the covariate was used to confirm the results from ANOVA.

RESULTS

Effects of SCH 23390, Raclopride, and Haloperidol on PR Responding

The effects of all three drugs on aspects of PR responding are shown in Table 1 and Fig. 1. SCH 23390 produced a substantial, dose-related suppression of PR responding. Number of lever presses were significantly reduced [Table 1; $F(4, 28) = 14.5$, $p < 0.001$] across the different drug treatments, and orthogonal analysis of trend demonstrated that there was a significant linear relation between dose and lever pressing, $F(1, 7) = 70.1$, $p < 0.001$. There also was a significant overall effect of drug treatment upon highest ratio completed [Fig. 1; $F(4, 28) = 10.9$, $p < 0.001$], and a significant linear relation between dose and highest ratio completed, $F(1, 7) = 31.0$, $p < 0.001$. Raclopride also produced a profound, dose-related suppression of responding on the PR schedule (Table 1; Fig. 1). There was a significant reduction in the number of lever presses [Table 1; $F(4, 24) = 8.4$, $p < 0.001$] across the different drug treatments, and a significant linear relation between dose and lever pressing, $F(1, 6) = 12.9$, $p < 0.02$. There was a significant overall effect of drug treatment upon highest ratio completed [Fig. 2; $F(4, 24) = 13.7$, $p < 0.001$], and a significant linear relation between dose and highest ratio completed, $F(1, 7) = 32.5$, $p < 0.001$. Haloperidol also produced a profound, dose-related suppression of responding on the PR schedule (Table 1; Fig. 1), with a significant reduction in the number of lever presses [Table 1; $F(4, 24) = 50.3$, $p < 0.001$] across the different drug treatments, and a significant linear trend, $F(1, 6) = 63.8$, $p < 9.02$. There was a significant overall effect of drug treatment upon highest ratio completed [Fig. 1; $F(4, 24) = 83.0$, $p < 0.001$], and a significant linear trend, $F(1, 6) = 251.7$, $p < 0.001$.

Analyses of time to complete the last ratio are shown in Fig. 2 (top). There were significant dose-related reductions in time to complete last ratio for SCH 23390, $F(4, 28) = 13.3$, $p < 0.01$, raclopride, $F(4, 24) = 2.9$, $p < 0.05$, and haloperidol, $F(4, 24) = 18.5$, $p < 0.01$. Figure 2 (bottom) is a cummulative reinforcer curve for an individual animal that received vehicle and 0.075 mg/kg haloperidol.

Effects of Accumbens DA Depletion

Rats receiving injections of 6-OHDA in the nucleus accumbens had significant depletions of DA in accumbens, but

TABLE 1

EFFECTS OF SCH 23390, RACLOPRIDE, AND HALOPERIDOL ON TOTAL NUMBER OF LEVER PRESSES

		Dose (mg/kg)			
	VEH	0.0375	0.075	0.15	0.3
SCH 23390					
Mean	1581.7	675.3	330.0	245.5	23.5*†
SEM	245.7	240.7	234.5	149.6	13.6
Raclopride					
Mean	1898.4	1143.1	763.7	427.9	42.5*†
SEM	440.7	338.7	220.1	204.5	19.4
Haloperidol					
Mean	1980.6	412.3	59.6	8.4	13.0*†
SEM	245.0	133.3	14.8	3.3	6.3*†

*$p < .005$, overall significant effect.
†$p < .005$, significant linear relation between dose and response.

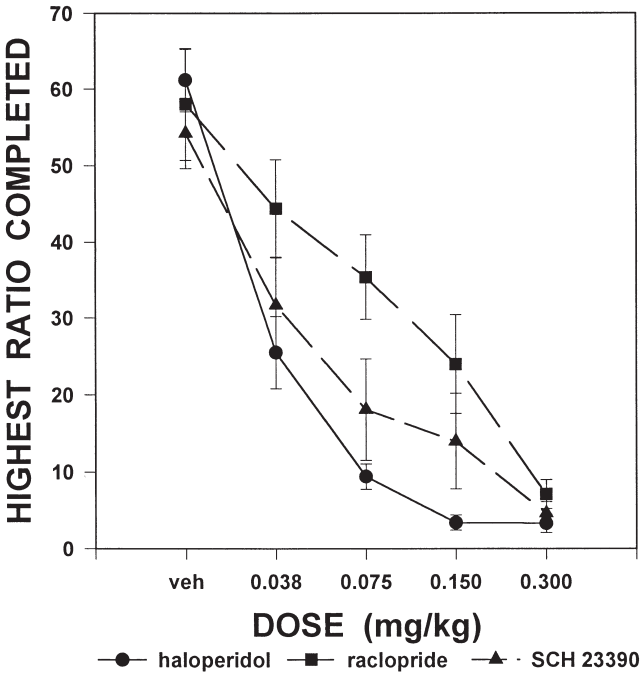

FIG. 1. Mean (+SEM) highest ratio completed for rats that received vehicle and different doses of SCH 23390, raclopride, and haloperidol.

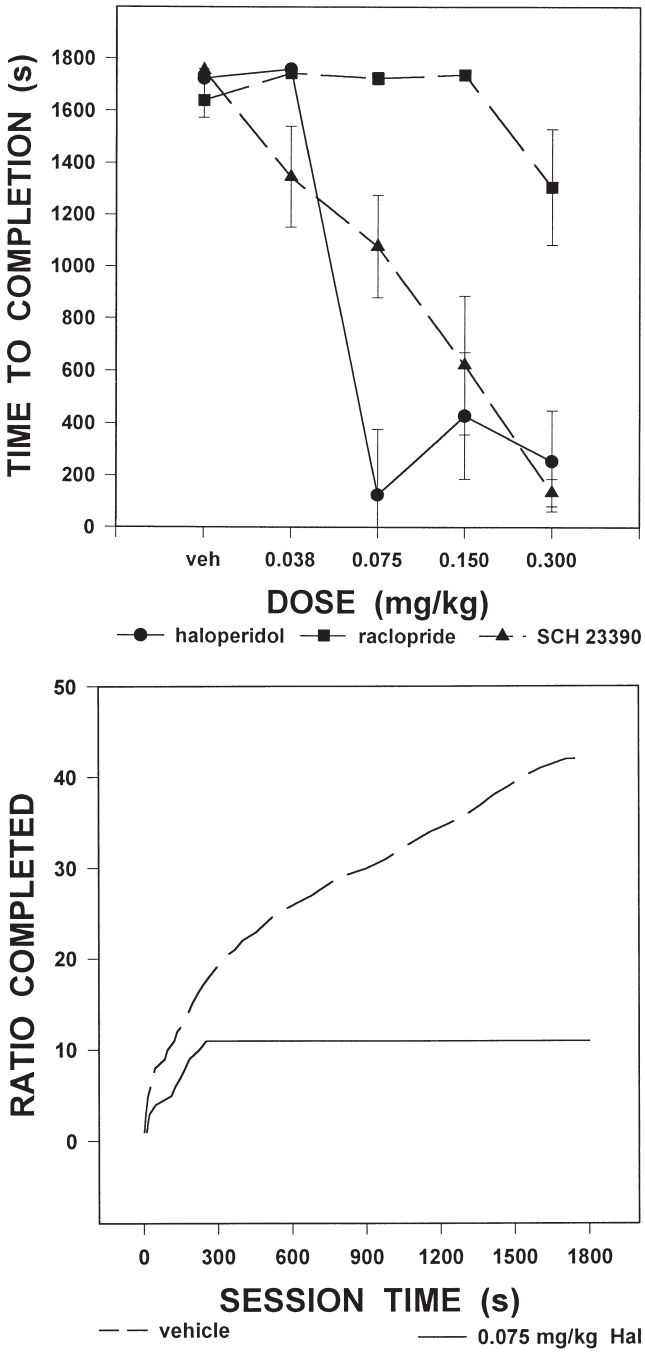

FIG. 2. Top: mean (+SEM) time to complete last ratio for rats that received vehicle and different doses of SCH 23390, raclopride, and haloperidol. Bottom: cumulative reinforcer curve for a representative individual rat. This curve is similar to a cumulative record, and shows the time within the session at which each ratio was completed. Under control conditions, the rat responded throughout the 30-min session, but injection of 0.075 mg/kg haloperidol caused the rat to "break" responding (i.e., cease responding before the end of the session).

not the VLS. Mean (± SEM) levels of DA (in ng/mg tissue) were as follows: nucleus accumbens, control—15.2 ± 1.1, 6-OHDA—1.9 ± 0.5 (12.5% of control levels, 6-OHDA different from control, $p < 0.05$); VLS, control—19.1 ± 1.8, 6-OHDA—21.3 ± 1.0 (111.5% of control levels, no significant difference between 6-OHDA and control groups). Accumbens DA depletions resulted in a severe and persistent disruption of PR responding. In Table 2, it can be seen that accumbens DA depletions reduced the total number of lever presses. There was a significant overall group difference between vehicle and DA-depleted rats, $F(1, 12) = 29.9$, $p < 0.001$. There was a significant overall effect of test week, $F(3, 36) = 4.2$, $p < 0.02$, and a significant group × week interaction, $F(3, 36) = 2.9$, $p < 0.05$. Analysis of simple main effects was used to determine if either group showed changes in responding across weeks. Although the vehicle group showed no changes over weeks, the group treated with 6-OHDA showed significant increases in number of responses over the 4 test weeks ($p < 0.05$). Orthogonal analysis of trend revealed that there was an interaction of the linear components in the two groups, $F(1, 12) = 8.7$, $p < 0.02$, indicating that the linear trends were different in the control and DA-depleted groups. Analysis of simple effects also revealed that there were significant differences between the vehicle and DA-depleted groups during the first 3 weeks after surgery ($p < 0.05$), but during week 4 the difference between these groups was not significant ($0.05 < p < 0.1$).

Accumbens DA depletions also substantially reduced the highest ratio completed (Fig. 3). There was a significant overall group difference between vehicle and DA-depleted rats, $F(1, 12) = 31.0$, $p < 0.001$. There was a significant overall effect of test week, $F(3, 36) = 5.6$, $p < 0.01$, and a significant group × week interaction, $F(3, 36) = 5.2$, $p < 0.01$. Analysis of simple main effects demonstrated that the DA-depleted group showed significant increases in highest ratio completed over the 4 test weeks ($p < 0.05$), but the vehicle control group did not. Orthogonal analysis of trend revealed that there was an interaction of the linear components in the two groups, $F(1, 12) = 8.7$, $p < 0.02$, demonstrating that the linear trends

TABLE 2
EFFECTS OF ACCUMBENS DA DEPLETIONS ON TOTAL NUMBER OF LEVER PRESSES IN EXPERIMENT THREE

Group	Week Postsurgery			
	Week 1	Week 2	Week 3	Week 4
Vehicle				
Mean	1805.7	1836.1	1750.2	1834.3
SEM	99.8	169.1	203.6	198.0
6-OHDA				
Mean	581.5	670.4	662.7	984.7
SEM	134.4	138.6	105.2	130.2

were different in the control and DA-depleted groups. There were significant group differences during the first 3 weeks of postsurgical testing ($p < 0.05$), but not during week 4. There were no significant differences in the baseline period (i.e., last 4 days of training) between the two groups [responses—control, 1563.0 ± 233.3, 6-OHDA, 1101.6 ± 154.6, $t(12) = 1.6$, $p > 0.1$; break point—control, 54.7 ± 4.0, 6-OHDA, 45.4 ± 1.2, $t(12) = 1.6$, $p > 0.1$]. Nevertheless, analysis of covariance with the baseline mean as covariate was used to account for baseline responding. In fact, the results of these analyses strongly confirmed the ANOVA results; for both behavioral measures there was a significant group difference [number of responses—$F(1, 11) = 30.8$, $p < 0.001$; highest ratio completed—$F(1, 11) = 23.9$, $p < 0.001$], and a significant group × week interaction [number of responses—$F(3, 33) = 4.4$, $p < 0.02$; highest ratio completed—$F(3, 33) = 5.6$, $p < 0.01$.

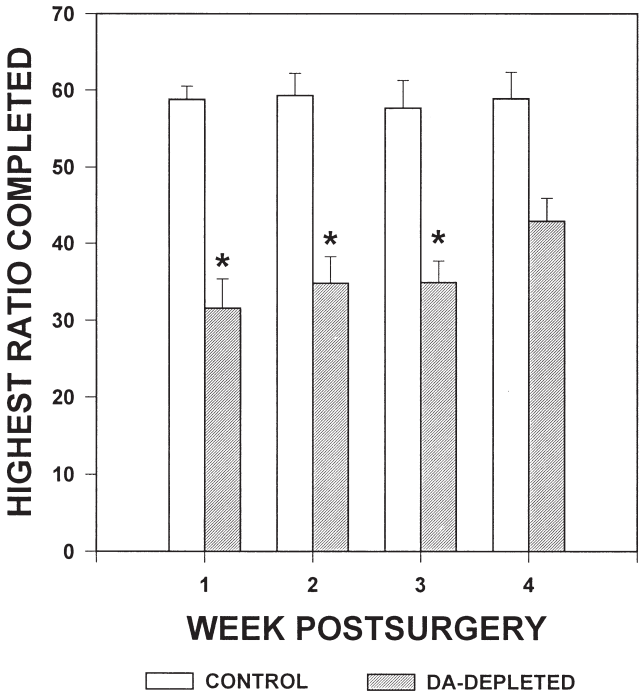

FIG. 3. Mean (+SEM) highest ratio completed per day for each of the 4 weeks of postsurgical testing for rats in the vehicle control group and rats that received intraaccumbens 6-OHDA (DA depleted). *$p < 0.05$, DA depleted significantly lower than control.

Analyses of time to complete the last ratio are shown in Fig. 4 (top). There were no significant differences between DA-depleted and control groups in weeks 2–4 after surgery; thus, data from only the first week postsurgery are shown (days 3–7). In week 1, there was a significant reduction in time to complete last ratio for DA-depleted rats, $F(1, 12) = 5.1$, $p < 0.05$. There also was a significant effect of day, $F(4, 48) = 5.8$, $p < 0.01$, and a significant depletion × day interaction, $F(4, 48) = 3.8$, $p < 0.01$. Analysis of simple effects for each day indicated that there was a significant difference between DA-depleted and control rats ($p < 0.05$) only on days 3 and 4 after surgery, which, along with the significant interaction, indicates a very rapid recovery of this measure. Figure 4 (bottom) is a cummulative reinforcer curve for an individual DA-depleted rat; this animal showed a substantial reduction in time to complete the last ratio on day 3 after surgery, but on day 7 this rat responded throughout the 30-min session.

DISCUSSION

The present experiments demonstrate that interference with DA transmission, either by administration of DA antagonists or depletion of accumbens DA, can substantially disrupt performance on the PR schedule for food reinforcement. The D_1 antagonist SCH 23390 and the D_2 antagonists raclopride and haloperidol were all very potent at suppressing PR responding and reducing the highest ratio completed. In view of the fact that SCH 23390 and raclopride are highly selective for their respective receptor subtypes, the present results indicate that suppression of PR responding is not related to the antagonism of one specific subtype of DA receptor. Rather, it appears that antagonism of receptors in either the D_1 or D_2 class will suppress PR responding, and drugs that have a high affinity for either receptor class will reduce PR responding in a potent manner. This pattern of results with D_1 and D_2 antagonists is similar to other studies of operant behavior (3,12). Although D_1 and D_2 receptors instigate different biochemical activities (23,33), and show distinct patterns of cellular distribution within the basal ganglia (14,57), it nevertheless appears that the effects of highly selective D_1 and D_2 antagonists on global features of food- reinforced PR responding are somewhat similar. As well as suppressing the number of responses, SCH 23390 and haloperidol substantially reduced the time to complete the last ratio, indicating that a break point had been reached. Raclopride significantly reduced time to complete the last ratio, although the magnitude of this effect appears to be less for raclopride than for the other two drugs. Many researchers have assumed that the PR break point is a measure of "reward" [e.g., (7)] or "reward strength" (17). However, evidence indicates that this measure is affected by several different conditions (31,55,56), including the kinetic requirements of the response (50). PR break points are, most directly, a measure of how much work an animal will perform to obtain access to a reinforcer (50,55). Thus, although it is clear that DA antagonists have profound effects on PR responding, the precise reasons for this effect remain unclear.

Neurotoxic depletions of DA in nucleus accumbens also produced significant reductions in PR responding. These results stand in marked contrast to earlier studies, in which it was reported that accumbens DA depletions had little or no effect upon responding on CRF (29,47), variable ratio 2.5 (37), fixed-interval 30 s (9), or variable-interval 30 schedules (52), as well as the food-reinforced component of a multiple

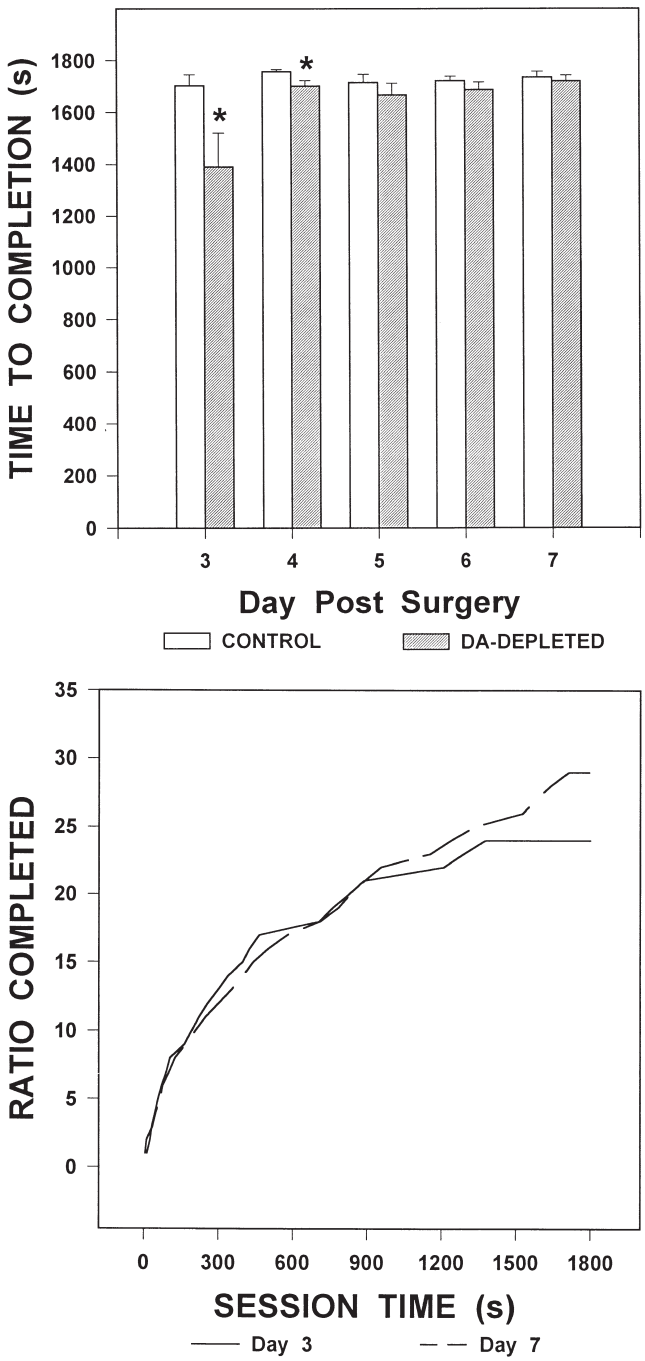

FIG. 4. Top: mean (+SEM) time to complete last ratio for rats in the vehicle control group and rats that received intraaccumbens 6-OHDA (DA depleted). Data for the first week of testing after surgery (days 3–7) are shown. *$p < 0.05$, DA depleted significantly lower than control on that test day. Bottom: cumulative reinforcer curve for a representative individual DA-depleted rat on day 3 and day 7 after surgery. On day 3 after surgery, the rat showed a "break" in responding (i.e., ceased responding before the end of the session). However, by day 7, the rat continued to respond throughout the session despite the fact that the animal completed fewer ratios than rats in the control group.

food/cocaine schedule (6). Thus, the present results, in combination with previous findings, indicate that the effects of accumbens DA depletions on food-reinforced responding vary greatly depending upon the schedule employed. In view of the fact that DA-depleted rats show preserved responding on some schedules, including the CRF, it appears as though accumbens DA depletions do not interfere with motivational or primary reinforcement processes that are common to all these diverse schedules. Rather, accumbens DA depletions have relatively selective effects on instrumental behavior, and the PR schedule is somewhat sensitive to those behavioral processes that are disrupted by DA depletion.

Following accumbens DA depletions, rats showed significant recovery of PR responding. Several lines of statistical evidence attest to this functional recovery. The significant group × week interaction and the interaction of the linear trends demonstrate that the DA-depleted group showed recovery over the test period. Although the control group did not show significant alterations in response number or highest ratio completed over the 4 test weeks, the DA-depleted rats significantly improved. In addition, the DA-depleted rats differed from the control group in the first 3 weeks of postsurgical testing, but not the fourth. Time to complete the last ratio showed a very rapid recovery, with DA-depleted rats failing to differ from the control group after the fourth day of postsurgical testing. These results are consistent with the literature showing recovery of function after DA-depleting brain lesions (65), including depletions of nucleus accumbens (46,61). Nevertheless, even as the recovery process is being emphasized, it is important to stress that the deficits in PR response output after accumbens DA depletions are relatively persistent compared to other studies of instrumental behavior. As noted in the introduction, injections of 6-OHDA into the same accumbens site as used in the present article did result in a slowing of the initial rate of CRF lever pressing (47). Yet these effects recovered by day 5 after surgery (47). In another study (46), it was reported that accumbens DA depletions similar to those produced here did reduce FR5 lever pressing; nevertheless, total number of responses recovered by the second week of postsurgical testing (46). Thus, the present results are noteworthy because of the relatively persistent nature of the effect of accumbens DA depletions. A few other studies have reported persistent effects of accumbens DA depletions on instrumental behavior. In a concurrent FR5/chow-feeding procedure, accumbens DA depletions decreased lever pressing but increased chow consumption, and this effect lasted for 2–3 weeks after surgery (10,11). Using a T-maze choice task, it was reported that accumbens DA depletions decreased barrier climbing for a high density of food reinforcement and increased locomotion to a lower density reward; this effect persisted for 3 weeks after surgery in two separate studies (8,44). Thus, it appears that procedures having a very high work requirement (i.e., the PR schedule), as well as those that offer choices between instrumental responses with different work requirements, are relatively sensitive to accumbens DA depletions, and the deficits that result can persist for several weeks after surgery. Although the time to complete the last ratio showed very rapid recovery in DA-depleted rats, it is possible that different schedule parameters (e.g., longer session, higher ratio increments) would lead to more persistent deficits on this measure.

PR responding can be affected by several different pharmacological and environmental conditions (31,50,55,56). Although motivational variables can affect PR responding, it is nevertheless an oversimplification to state that a reduction in

PR break point is only attributable to reductions in "reward." Indeed, PR responding is sensitive to changes in the kinetic requirements of the instrumental response, such as increases in lever height (50). Preliminary data from our laboratory indicates that PR responding also is sensitive to the placement of weights on the lever (unpublished observations). Moreover, there are several lines of evidence indicating that accumbens DA depletions do not produce a fundamental loss of appetite, or a reduction in the disposition to eat. It has generally been reported that accumbens DA depletions or intraaccumbens injections of DA antagonists do not affect food intake (2,25,48). Accumbens DA depletions had a minimal effect upon the total amount of food obtained by CRF lever pressing, which was significant only on day 3 after surgery (29,47); the effects on response patterning that did occur (i.e., initial slowing, slowing of the interresponse time distribution) did not resemble those of extinction (29,47). As noted above, with rats on a concurrent FR5/chow-feeding schedule, accumbens DA depletions or intraaccumbens injections of haloperidol decreased lever pressing but increased chow consumption (10,11,49). Accumbens DA depletions did not affect the discrimination of reinforcement magnitude, and failed to alter response selection based upon reinforcement magnitude, in a food-reinforced T-maze task (8,44). Thus, several studies indicate that rats with accumbens DA depletions remain directed toward the acquisition and consumption of food, provided that the work requirement is relatively low.

Several lines of evidence indicate that instrumental responding is an adaptation to constraint, and that work-related response costs affect the output of operant behavior (1,13,22,26, 27,35,38,43,53,54). It has been suggested that accumbens DA depletions affect the elasticity of demand for food, and make rats more sensitive to work-related response costs (43). Clearly, increasing ratio requirement by using the PR schedule reveals a deficit in instrumental response output in rats with accumbens DA depletions. Of course, the precise brain mechanisms that underlie this effect are unclear. It is possible that accumbens DA depletions produce subtle motor effects [e.g., slowing of response initiation, see (46,47)] that make lever pressing difficult and ultimately lead the animals to stop responding. Accumbens DA could be involved in the exertion of effort, or in overall energy expenditure (10,32,39–43,58). Alternatively, accumbens DA depletions could decrease the ability of conditioned stimuli to instigate responding, which would make it very difficult for animals to emit very large ratios (36,40–43). Finally, it is possible that nucleus accumbens participates in the process that regulates response allocation. Continued research will be necessary to precisely identify the behavioral effects of accumbens DA depletions, and to determine the involvement of different subregions of accumbens [i.e., core and shell; see (4,15,18,20,21,28,30,34,52,59,62,63,64] in PR responding.

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