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Nucleus Accumbens Dopamine Depletions and Time-Constrained Progressive Ratio Performance: Effects of Different Ratio Requirements

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HAMILL, S., J. T. TREVITT, K. L. NOWEND, B. B. CARLSON AND J. D. SALAMONE. *Nucleus accumbens dopamine depletions and time-constrained progressive ratio performance: Effects of different ratio requirements.* PHARMACOL BIOCHEM BEHAV **64**(1) 21–27, 1999.—Two experiments were conducted to determine the effects of accumbens dopamine (DA) depletions on progressive ratio responding for food reinforcement. In one version of this schedule, ratio requirement increased by one response after each reinforcer was obtained (PROG1). In the other version, ratio requirement increased by five responses after each reinforcer was obtained (PROG5). For both versions, 60-min sessions were conducted. Accumbens DA depletions produced by local injections of 6-OHDA substantially decreased the number of responses on both schedules. The deficits in the response number induced by DA depletions persisted through the two weeks of postsurgical testing for both the PROG1 and PROG5 schedules. However, there were differences between the effects of DA depletions on the two schedules in terms of the time to complete the last ratio. Although time to complete the last ratio was significantly reduced by DA depletions only in the first week of testing on the PROG1 schedule, rats recovered on this measure by the second week after surgery. In contrast, DA-depleted rats on the PROG5 schedule showed a more persistent suppression of the time to complete the last ratio, which lasted through both weeks of postsurgical testing. Performance on schedules that generate low baseline rates of responding (e.g., continuous, fixed, and variable interval) is relatively unaffected by accumbens DA depletions; nevertheless, accumbens DA depletions substantially impair progressive ratio response output. The high work output necessary for responding on the PROG5 schedule may make these animals more sensitive to the effects of accumbens DA depletions. © 1999 Elsevier Science Inc.

Dopamine Reinforcement Operant Motivation Progressive ratio Movement Behavioral economics

DOPAMINE (DA) in nucleus accumbens has been implicated in various processes related to instrumental performance. Some researchers have suggested that DA in nucleus accumbens mediates the positive reinforcing effects of natural stimuli such as food (14,38,45), as well as drugs of abuse (6). Yet, despite the popularity of this view, there is considerable evidence against the idea that accumbens DA mediates the primary reinforcing or motivating characteristics of natural reinforcers such as food. Fundamental aspects of food motivation, such as food intake and discrimination of different magnitudes of food reinforcement, are not substantially affected by accumbens DA depletions or injections of haloperidol into the accumbens (4,19,34). Responding on a continuous-reinforcement (CRF) schedule is highly dependent upon food motivation [e.g., (2,35)], yet CRF lever pressing is relatively unaffected by accumbens DA depletions (21,33), and the alterations in response patterning that are shown after DA depletions (i.e., relative lack of high rate interresponse times, initial slowing) differ substantially from the effects of extinction (21,33). Accumbens DA depletions had little or no effect on responding supported by variable and fixed-interval 30-s schedules (9,39). It has been demonstrated that accumbens DA depletions that substantially altered cocaine-reinforced responding had little effect upon food-reinforced responding (6,25). In fact, comparisons of the effects of DA depletions in different terminal regions have shown that de-

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pletions in the ventrolateral striatum, and not the nucleus accumbens, tend to have profound effects on lever pressing (9,32).

Although accumbens DA depletions do not generally produce severe deficits in instrumental responding across a broad range of schedules, the effects of accumbens DA depletions interact with the work requirements of the instrumental task [(8,10,11,31,35,39); for reviews, see (26–30)]. Experiments that offered choices between responses with different work requirements have shown that accumbens DA depletions alter the relative allocation of instrumental responding. Rats with DA depletions 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 (8,10,11,30,35). These data indicate that rats with accumbens DA depletions remain directed toward the acquisition and consumption of food, but are sensitive to work-related response costs (28–31,35). In addition, it appears as though the effects of accumbens DA depletions on lever pressing procedures substantially depend on the baseline response rate generated by the schedule. It has been reported that fixed-ratio 5 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 (32,39). Across different types of ratio schedules (FR1, 4, 16, 64), increasing response output by increasing ratio requirement made rats much more sensitive to the effects of accumbens DA depletions (2).

The present investigation was a part of a larger series of studies, which has focused upon the effects of accumbens DA depletions across a broad range of schedules that generate various rates and distinct patterns of responding (29). One schedule that typically generates a high rate of responding is the progressive ratio (PROG) schedule. With this schedule, the ratio requirement is increased as the animal completes each ratio. Typically, rats respond to this incremental ratio requirement by emitting a very large number of responses. As noted in a review by Stewart (42), there are several different types of PROG schedules, and previous work has involved both open-ended and time-constrained schedules. An animal responding on an open-ended PROG schedule proceeds through a ratio progression until it reaches the "break point" and ceases responding. Despite the fact that some researchers have assumed that the PROG break point is a measure of "reward" [e.g., (7)], or "reward strength" (15), it is important to emphasize that this measure is affected by several different conditions (22,42,43), including the kinetic requirements of the response (36,37). A recent article reported the effects of excitotoxic lesions of nucleus accumbens of PROG responding (5). Previous work from our laboratory examined the effects of accumbens DA depletions on the performance of a PROG schedule with a 30-min time constraint, in which the response requirement increased by 1 for each ratio (PROG1). This schedule generated high rates of responding (i.e., 1500–2000 per 30 min), and accumbens DA depletions substantially suppressed the total number of lever presses emitted (1). However, another measure of performance was the time to complete the last ratio, which is defined as the time within the session at which the animals receive their last reinforcer. Although not directly a measure of response output, a reduced time to complete the last ratio is reflective of either pauses in lever pressing, or cessation of responding, at the end of the session. In our previous work, time to complete the last ratio was dramatically suppressed by DA antagonists, but was only transiently affected by accumbens DA depletions (1). In the present study, a 60-min session time was used rather than a 30-min session, because it was thought that the 60 min session time would allow for the assessment of response rate in a time-constrained schedule, yet would be long enough to allow for a more sensitive assessment of the time to complete the last ratio. In addition, the effects of accumbens DA depletions on PROG1 performance were compared with effects on a PROG5 schedule, in which the ratio requirement increases by five responses after each reinforcement. It was hypothesized that the PROG5 schedule would be more sensitive to the effects of accumbens DA depletions than the PROG1 schedule. For both studies, the rats were trained prior to surgery, so that the present work focused upon the effects of DA-related manipulations on PROG performance in rats that were well trained.

METHOD

Subjects

A total of 42 male Sprague–Dawley rats (Harlan–Sprague–Dawley, Indianapolis, IN) were used for both 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. Water was available ad lib 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 PROG schedule. For the present experiments, the PROG1 schedule began with a ratio value of 1, and then the ratio requirement increased by one response after each completed ratio. The PROG5 schedule began with a ratio value of 5, and the ratio requirement increased by five responses with each additional ratio completed. The sessions lasted 60 min, and a computer recorded the total number of responses, the time to complete each ratio, the average interresponse time 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 or showed long pauses at the end of the session [see also (1)]. Training proceeded 5 days a week for approximately 12 weeks for both PROG schedules before any surgeries were conducted.

Drugs

Sodium pentobarbital (50.0 mg/kg) was used as the anesthesia for surgery.

DA Depletion by Injection of 6-OHDA

Injections of 6-OHDA into the nucleus accumbens were performed with the rats under pentobarbital anesthesia, and all rats received injections of 20.0 mg/kg pargyline (IP) 30 min prior to surgery. Desipramine was not used because we have observed that the combination of pargyline and desipramine caused feeding deficits in some control animals. Bilateral in-

jections of 6-OHDA (Research Biochemicals Inc., Natick, MA) were performed with 30-gauge stainless steel injectors stereotaxically placed into the nucleus accumbens (AP + 2.8 mm, MI ± 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 on each side. Rats receiving the control treatment 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. This low flow rate was used to minimize damage to the local area and reduce spread to more dorsal regions. The injector was left in place for 2 min after the injection was completed.

Neurochemical Analyses for Tissue Dopamine

After completion of the experiments, rats were placed into a carbon dioxide chamber for 30 s and decapitated, after which their brains were quickly removed and frozen. A stainless steel tube (18 gauge) was used to dissect tissue samples (i.e., "tissue punches") from 0.75 mm-thick coronal sections through the nucleus accumbens and the ventrolateral striatum (VLS). Tissue samples form each region were placed in 200 μl of chilled 0.1 N perchloric acid, homogenized, centrifuged, and frozen. The samples were later thawed, 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 (ion pairing agent) to 1.0 liters of mobile phase. Standards of DA (Sigma Chemical Co.) were assayed before, during, and after the tissue samples.

Experimental Procedures

Separate groups of rats were trained on the PROG1 and PROG5 schedules for approximately 12 weeks (5 days per week, 60-min sessions) prior to surgery. In the PROG1 experiment, rats received intracranial injections of either ascorbate vehicle (n = 11) or 6-OHDA (n = 12) into the nucleus accumbens as described above. For the PROG5 experiment, seven rats received vehicle injections, while 12 rats received injections of 6-OHDA. Rats were tested on their respective PROG schedules, 5 days per week, for 2 weeks (60-min sessions on days 3–7 and 10–14 postsurgery). Rats received additional lab chow in their home cages at least 1 h after the operant sessions to maintain body weight. After completing the behavioral testing, rats were decapitated for DA assays as described above.

Statistical Analyses

On the last baseline training day, rats assigned to the vehicle and 6-OHDA groups in both experiments did not differ from each other in terms of number of responses or time to complete the last ratio (see figs. 1–4). Because of the variability in baseline responding, inferential statistics were performed with analysis of covariance (ANCOVA; Systat 5.0), using number of responses and time to complete the last ratio on the final baseline training day as the covariate. Postsurgical data for both behavioral measures (number of responses and time to complete last ratio) were blocked into two weekly means (i.e., days 3–7, days 10–14) for each animal, as in previous studies (2,10,11,32). Each ANCOVA had a 2 group × 2 week factorial design, with repeated measures on the week factor. If there was an interaction, analysis of simple main effects (18) was used to analyze the sources of the interaction effect. Rats that received 6-OHDA injections were only included in the DA depleted groups if they had accumbens DA levels less than 17% of the mean control value in each experiment. Thus, for the PROG1 experiment, six rats had DA depletions that met the criterion, while 5 rats met the depletion criterion in the PROG5 experiment. As in previous studies (32), correlational analyses also were performed, in which all rats that received 6-OHDA, including those that did not meet the depletion criterion, were included.

RESULTS

Baseline Performance on the PROG1 and PROG5 Schedules

Various parameters of baseline performance (i.e., final baseline day) on the PROG1 and PROG5 schedules are shown in Table 1. Rats on the PROG1 schedule tended to emit more responses than rats on the PROG5 schedule, although rats responding on PROG5 achieved higher ratios. Time to complete the last ratio generally approached the last few minutes of the 60-min (i.e., 3600 s) sessions for both schedules.

Behavioral Effects of Accumbens DA Depletion

Only rats that met the DA depletion criterion (i.e., <17% of control values) were included in the ANCOVA analyses of behavioral results (see next section for analyses of the neurochemical data). Accumbens DA depletions resulted in a substantial and persistent disruption of both PROG1 and PROG5 responding. Figures 1 and 2 show the results of the PROG1 study. In Fig. 1, it can be seen that total number of lever presses was suppressed by DA depletion. ANCOVA revealed that there was a significant overall group difference between vehicle and DA-depleted rats, $F(1,14) = 8.1$, $p <$

TABLE 1

COMPARISON OF BASELINE RESPONDING ON THE PROG1 AND PROG5 SCHEDULES

Parameter	PROG1	PROG5
Number of responses mean (SEM)	4350.1 (338.2)	2667.7 (399.8)
Highest ratio completed mean (SEM)	94.4 (4.0)	153.7 (12.9)
Time to completion (s) mean (SEM)	3453.4 (23.3)	3345.3 (84.7)

PROG1, n = 13; PROG5, n = 12; data are combined for animals assigned to the vehicle and 6-OHDA treatment groups in each study.

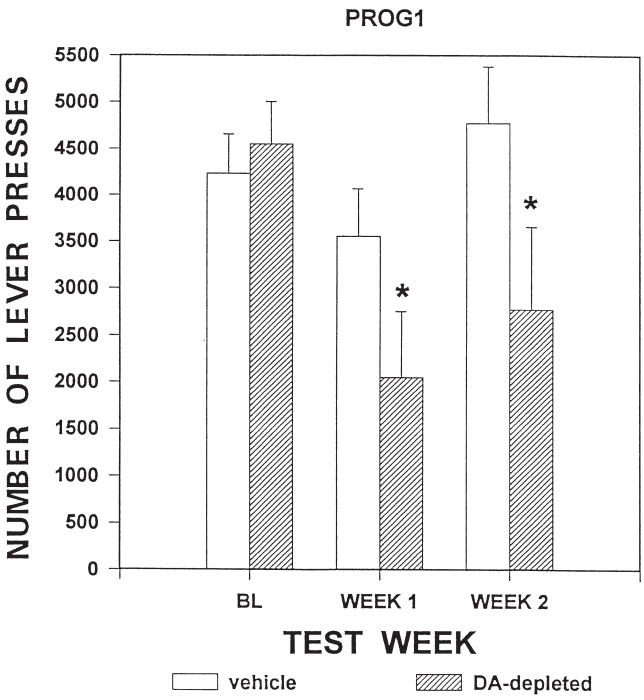

FIG 1. PROG1. Mean (+SEM) number of responses completed per day for each of the 2 weeks of postsurgical testing, and the last baseline day (BL), for rats in the vehicle control group and DA-depleted rats. *$p < 0.05$, DA-depleted significantly lower than control.

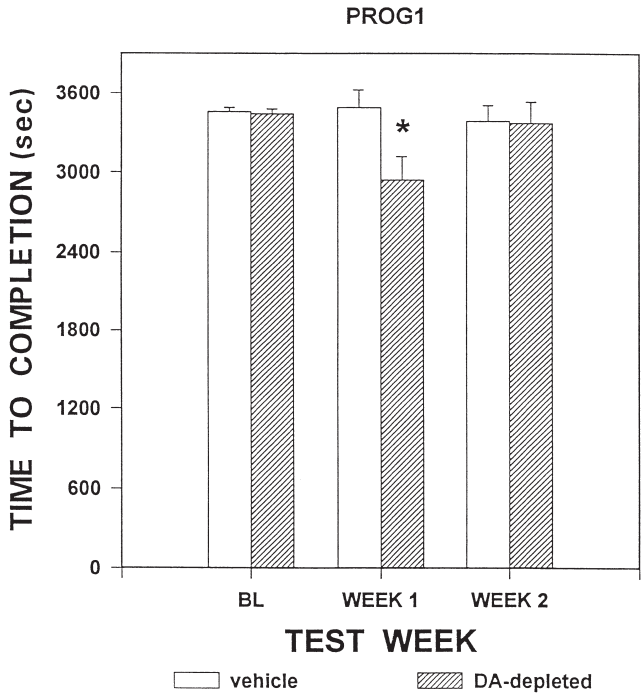

FIG 2. PROG1. Mean (+SEM) time to complete last ratio for rats in the vehicle control group and DA-depleted rats. Data for the last baseline day (BL), and the 2 weeks of testing after surgery, are shown. *$p < 0.05$, DA-depleted significantly lower than control during that test week.

0.02). There was no significant overall effect of test week, $F(1, 14) = 2.2$, NS, and no significant group × week interaction $F(1, 14) = 0.05$, NS. Time to complete the last ratio also was affected by DA depletion (Fig. 2). There was a significant effect of DA depletion, $F(1, 14) = 5.0$, $p < 0.05$, but no significant effect of test week, $F(1, 14) = 0.016$, NS. There was a significant DA depletion × week interaction, $F(1, 14) = 7.5$, $p < 0.02$. Analysis of simple main effects was used to determine the source of the interaction effect; there was a significant difference between DA-depleted and control animals in time to complete the last ratio during the first week postsurgery, but not during the second week (Fig. 2). In Figs. 3 and 4, the results of the PROG5 study are shown. As in the first experiment, total number of lever presses on the PROG5 schedule was suppressed by DA depletion (Fig. 3). ANCOVA showed that there was a significant overall group difference between vehicle and DA-depleted rats, $F(1, 9) = 9.0$, $p < 0.02$, significant effect of test week, $F(1, 9) = 0.036$, NS, and no significant group × week interaction, $F(1, 9) = 1.67$, NS. Data on time to complete the last ratio for the PROG5 experiment are depicted in Fig. 4. There was a significant effect of DA depletion, $F(1, 9) = 9.0$, $p < 0.02$, no significant effect of test week, $F(1, 9) = 0.5$, NS, and, unlike the previous experiment, there was no significant DA depletion × week interaction, $F(1, 9) = 0.6$, NS.

Neurochemical Effects of Accumbens DA Depletions

Table 2 shows the results of the HPLC analyses of tissue DA content. Rats treated with 6-OHDA that met the depletion criteria significantly differed from the control group in terms of levels of DA in accumbens (*t*-test, $p < 0.05$), but not the VLS, for both the PROG1 and PROG5 experiments. However, correlational analyses also were performed, which included animals that received 6-OHDA but did not meet the DA depletion criterion. If the mean number of responses in the first week after surgery were expressed as a percent of baseline responding, there was a significant correlation between the lever-pressing output and tissue levels of accumbens DA across all rats treated with 6-OHDA (PROG1, $r = 0.73$, $p < 0.05$; PROG5, $r = 0.58$, $p < 0.05$). Thus, rats with greater DA depletions had a more substantial suppression of responding than 6-OHDA–treated rats with moderate DA depletions.

DISCUSSION

Accumbens DA depletions suppressed lever-pressing output on both the PROG1 and PROG5 schedules. For both schedules, baseline rates of responding were moderately high (i.e., >2400 responses per 60 min). This value is approximately the same as response rates previously shown by FR4 or FR5 schedules (2,32), although it is somewhat lower than the baseline rate of responding shown for the FR64 schedule [2500–3500 responses per 30 min, see (2)]. In the present study, the PROG1 schedule tended to generate higher rates of responding, although the suppressive effects of accumbens DA depletions on total response output were similar for both schedules. Accumbens DA depletions suppressed responding by about 40% relative to the control group, and the deficits in responding produced by DA depletions persisted for 2 weeks after surgery. These results are consistent with the results of

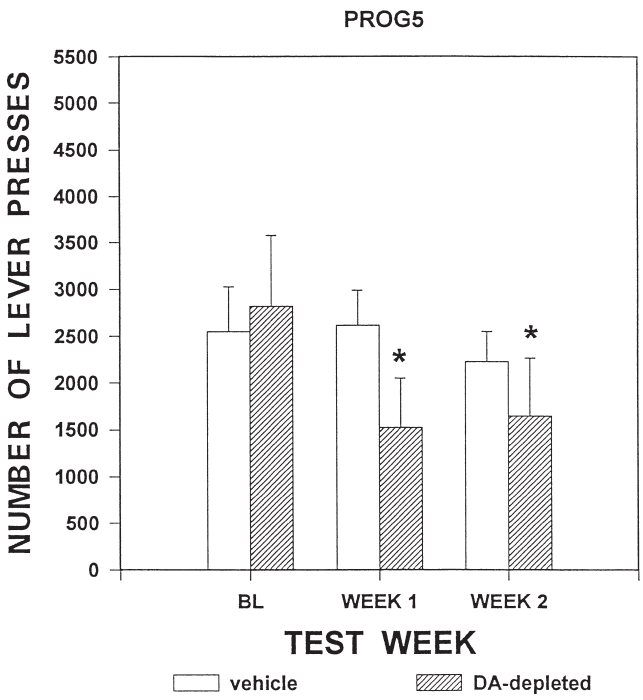

FIG 3. PROG5. Mean (+SEM) number of responses completed per day for the baseline day (BL) and the 2 weeks of postsurgical testing, for rats in the vehicle control group and DA-depleted animals. *$p <$ 0.05, DA-depleted significantly lower than control.

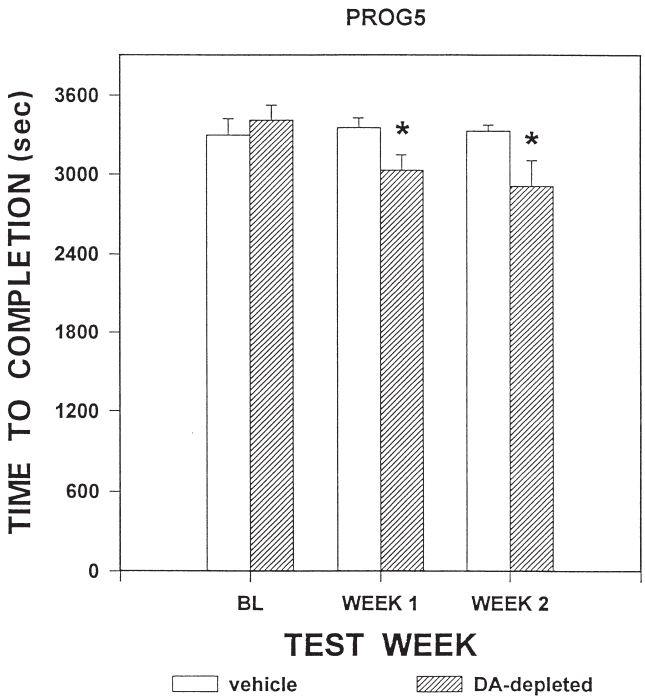

FIG 4. PROG5. Mean (+SEM) time to complete last ratio for rats in the vehicle control group and rats that received intraaccumbens 6-OHDA (DA-depleted); data from baseline (BL) and 2 weeks of postsurgical testing are shown. *$p < 0.05$, DA-depleted significantly lower than control during that test week.

an earlier study of PROG1 responding (1). In addition, these results are consistent with the general observation that the effects of accumbens DA depletions on lever pressing depend upon the baseline rate generated by the schedule (2,39). Schedules that generate only 300–600 responses per 30 min (e.g., CRF, fixed and variable interval 30 s) show little or no effect after accumbens DA depletions, while schedules that generate moderately high rates (e.g., FR4, FR5, PROG1, PROG5) are substantially impaired by accumbens DA depletions, and schedules generating very high rates (e.g., FR64) are severely impaired (1,2,9,21,32,33,39; see review in (29)].

In the present study, the effects of 6-OHDA on PROG level pressing were highly dependent upon the degree of DA depletion. For both the PROG1 and PROG5 studies, there were significant positive correlations between the number of lever presses in the first week of postsurgical testing (as percent of baseline) and the levels of DA in accumbens. Animals with substantial DA depletions (i.e., less than 17% of control levels) showed reductions in PROG responding, but many of those with modest depletions did not. Similar results have been reported previously. In one study of FR5 responding, the entire group of rats that received 6-OHDA into accumbens had only a mild DA depletion, and did not show a significant reduction of FR5 responding; nevertheless, there was a significant correlation between lever pressing and DA levels (10). In a more recent study, levels of DA in the accumbens core after injections of 6-OHDA were found to be correlated with the suppression of FR5 responding (39). The relation between DA levels and the degree of impairment also varies, depending upon the DA terminal region into which the 6-OHDA is injected. Injections of 6-OHDA into VLS suppressed FR5 responding, and the behavioral deficit was correlated with the degree of DA depletion (33). Yet, with VLS injections, the deficits produced were much more severe than with accumbens DA depletions, and even rats with mild DA depletions in VLS (e.g., 40% of control levels) still showed substantial reductions in lever pressing (33). Thus, the results of several studies indicate that the effects of 6-OHDA injections on lever pressing depend upon the site of injection, the

TABLE 2

DA CONTENT (IN ng DA/mg TISSUE) IN NUCLEUS ACCUMBENS AND VENTROLATERAL STRIATUM FOR VEHICLE–TREATED AND DA-DEPLETED RATS

		Region	
Group		Accumbens	VLS
PROG1			
vehicle	mean	6.1	8.4
	SEM	0.8	1.2
DA-depleted	mean	0.5*	9.9
	SEM	0.1	1.3
PROG5			
vehicle	mean	4.3	11.8
	SEM	0.1	0.7
DA-depleted	mean	0.4*	14.0
	SEM	0.1	0.8

*$p < 0.05$, different from vehicle group.

schedule being tested, and the degree of DA depletion that is produced.

Although the effects of DA depletions on total number of responses were similar for both schedules, a different pattern of effects was observed with the other behavioral measure, i.e., time to complete the last ratio. The distinct pattern of effects of DA depletions on the two different schedules makes it unlikely that accumbens DA depletions reduced time to complete the last ratio because of effects on processes that are common to both schedules (e.g., temporal estimation of the session time). Reductions in the time to complete the last ratio reflect the fact that DA-depleted rats are spending more nonreinforced time at the end of the session, during which they either take longer postreinforcement pauses, take longer pauses in lever pressing within ratios [i.e., long interresponse times, see (32)], or stop responding altogether. Previous work has employed this measure of responding to characterize performance on the PROG1 schedule. The DA antagonists, haloperidol, raclopride, and SCH 23390, dramatically reduced the time to complete the last ratio in rats responding on a 30-min PROG1 schedule (1). However, in that study, accumbens DA depletions only suppressed time to complete the last ratio for the first few days after surgery (1). In the present work, despite the fact that a 60-min session time was used, accumbens DA depletions produced only a transient effect on time to complete the last ratio on the PROG1 schedule. DA-depleted rats only differed from rats in the control group during the first week of post surgical testing (Fig. 2). In contrast, on the PROG5 schedule, DA depletions produced a deficit in time to complete the last ratio that persisted throughout both weeks of postsurgical testing. Thus, attaching an additional ratio requirement (i.e., a five-response progression rather than one) on the PROG schedule led to a more persistent effect of accumbens DA depletions in terms of the time to complete the last ratio.

Instrumental responding is a complex, multifactorial phenomenon. Response output on different schedules results from an interaction of several factors, including previous learning, motivational conditions such as food deprivation and reinforcement density, and also response constraints such as ratio value or other forms of work requirement (13,16,17, 20,24,40,41). Thresholds for lever pressing to receive brain stimulation are affected by stimulation parameters, but also by ratio requirement (12). PROG breakpoints are affected by food deprivation, but also by the height of the lever (36,37). Thus, it is difficult to precisely determine the functional significance of impairments induced by brain manipulations, such as DA depletions. As noted in a recent review (3), no single operant schedule, including the PROG, can quantify all aspects of instrumental behavior. Nevertheless, across a number of studies involving a broad range of schedule conditions, several generalizations can be made. The effects of accumbens DA depletions do not closely resemble the effects of extinction (21,33) or prefeeding to reduce food motivation (2,35). Accumbens DA depletions have effects that are highly dependent upon the baseline response rate generated by the schedule (2,29,39). In addition, ratio requirements exert a powerful influence over the magnitude and persistence of deficits produced by accumbens DA depletions [(2); present study]. Taken together, these results support the notion that rats with accumbens DA depletions do not have a general loss of appetite or food motivation, but instead, have some difficulty with behavioral activation, or the ability to overcome response constraints (23,26–29,44).

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