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The Effects of Nucleus Accumbens Dopamine Depletions on Continuously Reinforced Operant Responding: Contrasts With the Effects of Extinction

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SALAMONE, J. D., P. KURTH, L. D. McCULLOUGH AND J. D. SOKOLOWSKI. *The effects of nucleus accumbens dopamine depletions on continuously reinforced operant responding: Contrasts with the effects of extinction.* PHARMACOL BIOCHEM BEHAV **50**(3) 437–443, 1995.—Two experiments were undertaken to study the role of nucleus accumbens dopamine (DA) in instrumental lever pressing on a continuous reinforcement schedule (CRF). In the first experiment, the neurotoxic agent 6-hydroxydopamine was infused directly into the nucleus accumbens to investigate the effects of DA depletion on lever pressing performance. DA depletion had only a modest effect on the total number of lever presses, and there was a significant effect on total lever presses only on the first test day (third day postsurgery). Analyses also were performed on responding across the 45-min session by breaking down the session into three 15-min periods. During the test session on day 3 postsurgery, there was a significant group × time interaction, with DA-depleted rats showing a significant reduction in the numbers of responses in the first 15-min period, but no significant effects over the second or third 15-min period within the session. Although control rats showed a within-session decline in responding, the DA-depleted rats did not. In addition, analysis of interresponse times (IRTs) indicated that accumbens DA depletions produced a slowing of the local rate of responding as indicated by a significant decrease in high rate (i.e., short-duration IRT) responses and an increase in low rate (i.e., long-duration IRT) responses. In a second experiment, the effects of extinction on CRF performance were investigated. Unlike the effects of nucleus accumbens DA depletion, extinction produced lower levels of responding throughout the entire test session. In contrast to the effects of accumbens DA depletions, analysis of IRTs indicated that extinction produced a significant increase in high-rate responses (low IRTs), which is probably indicative of an extinction "burst." These results indicate that accumbens DA depletions produce a response slowing that does not closely resemble the effects of extinction.

Nucleus accumbens Dopamine Motivation Operant behavior Behavioral activation Reinforcement Extinction Motor

CONSIDERABLE evidence indicates that dopamine (DA) has some involvement in the performance of appetitively motivated behavior. Nevertheless, there continues to be uncertainty about the precise nature of dopaminergic involvement in appetitively motivated instrumental responding. Several studies have shown that systemic administration of DA antagonists impairs positively reinforced instrumental responses [for reviews see (29,31,33,45)], and it has been suggested that DA systems are important for mediating the reinforcing or "hedonic" effects of rewarding stimuli (45–47). Although DA is present in several different terminal regions, DA in nucleus accumbens has received particular emphasis in regard to the hypothesized involvement of DA in reinforcement processes (7,13). Nucleus accumbens DA has been implicated in a number of behavioral functions related to appetitive motivation (3–6,10,14,18,21,22,26,36). Considerable research has focussed upon studies of drug reinforcement processes (7,13,42). Moreover, several studies have shown that accumbens DA release or metabolism is increased during the performance of appetitive tasks (4,19,24,34).

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Despite the emphasis placed upon the involvement of accumbens DA in reinforcement processes, there have been very few studies focussing on the role of accumbens DA in responding on simple schedules of reinforcement involving natural reinforcers such as food. One important schedule to examine is continuous reinforcement (CRF), which represents a fundamental reinforcement condition in which there is primary positive reinforcement. It has been reported that rats pressing a lever on a CRF schedule for food reinforcement showed increases in extracellular DA in nucleus accumbens as measured by in vivo microdialysis (13,18). Additional analyses have shown that these increases in accumbens DA release were highly correlated with the number of lever pressing responses (18). Depletion of nucleus accumbens DA by injections of the neurotoxic agent 6-hydroxydopamine (6-OHDA) was shown to produce a minor reduction in CRF responding (18). In this previous study, it was reported that accumbens DA depletions did not produce an extinction-like within-session decline in responding (18). This finding is potentially important in view of the suggested similarity between the effects of DA antagonism and extinction (45–47). Thus, the present series of experiments was undertaken to provide a detailed characterization of the behavioral effects of accumbens DA depletions, and to compare and contrast those results with the effects of extinction on CRF performance. To provide a more complete characterization of the behavioral effects of DA depletion and extinction, the behavioral testing was controlled by a computer program that recorded the interresponse time (IRT) for each response. The IRT is the time between each operant response, and thus this measure represents the reciprocal of the local response rate. Analysis of IRTs has been used previously to characterize the behavioral effects of DA depletions on instrumental responding (35,38). For the first experiment, DA in nucleus accumbens was depleted by local injections of 6-OHDA to assess the effects of DA depletion on CRF performance. In the second experiment, unoperated rats received similar training as that used for Experiment 1, and were subsequently exposed to an extinction session.

METHOD

Animals

A total of 27 male Sprague-Dawley rats (Harlan Sprague-Dawley, Indianapolis, IN) were used for these experiments. They were group housed in a colony that was maintained at 23°C and that had a 12L : 12D cycle (lights on 0700).

Behavioral Procedures

For all experiments, testing was performed in operant chambers (28 × 23 × 23 cm), and the rats were food deprived to 85% of their free-feeding body weight. On the first day of training, rats were placed in the operant chamber for 20 min and were given 4.0–5.0 g of 45-mg Bioserve pellets (Frenchtown, NJ) and small pieces of lab chow in the food dish. On the second and third day, rats were magazine trained and received a pellet every 30 s for 45 min. Next, all rats were trained on the CRF procedure in 45-min sessions, with all rats receiving a total of seven 45-min CRF sessions over a 2-week period before the experiments began. All rats were emitting 200 or more lever press responses by the end of the last training session. For both experiments a computer program was used to analyze the pattern of responding by counting the total number of responses for the entire 45-min session, and also recording responses across the test session in three 15-min periods. In addition, the time between each response (i.e., the IRT) was recorded and stored by the computer program. Based upon the IRT data, each response was counted as belonging to one of eight IRT time bins: 0–1.5 s, 1.5–3.0 s, 3.0–4.5 s, 4.5–6.0 s, 6.0–7.5 s, 7.5–9.0 s, 9.0–12.0 s, and > 12.0 sec.

Accumbens DA Depletion by Injection of 6-OHDA

In Experiment 1, accumbens DA was depleted by bilateral injection of 6-OHDA into the nucleus accumbens (AP +2.8 mm, ML ±1.4 mm, V −7.8 mm) with the rats under pentobarbital anesthesia. These coordinates correspond to the "core" region of the nucleus accumbens [see (48,49)]. A total of 12.5 μg of the free base of 6-OHDA dissolved in 0.1% ascorbic acid was injected per side (2.5 μl of 5.0 μg/μl 6-OHDA). A 30-ga injector was used, and a Harvard Apparatus syringe pump delivered the injections at a flow rate of 0.75 μl/min. Control injections consisted of 2.5 μl of the 0.1% ascorbate solution at the same site as 6-OHDA-treated rats. Two minutes were allowed for diffusion into the tissue before the injectors were removed. Rats were not injected with pargyline or desipramine prior to surgery as in previous studies [see (17)] because pilot studies indicated that this treatment affected IRT distributions in control rats.

Neurochemical Analysis of DA

After Experiment 1, rats were decapitated and their brains were removed and frozen. Coronal sections 1.0 mm thick were cut through the brain, and samples of prefrontal cortex, nucleus accumbens, and striatum were dissected from successive coronal sections. The tissue samples were placed in 200 μl of 0.1 N perchloric acid, homogenized, and centrifuged, and the supernatant (10-μl samples from each tube) was used for neurochemical analyses. These analyses employed a high performance liquid chromatography (HPLC) system, which consisted of a Waters dual-piston pump, a precolumn filter, a reverse-phase column, a Coulochem electrochemical detector, and a chart recorder. The mobile phase was a phosphate buffer (pH 4.5) with 7.0% methanol and 2.6 ml of sodium octyl sulphate. An oxidation potential of 0.2 V (working vs. reference electrode) was used for electrochemical detection. Standards of DA were assayed before, during, and after the samples (Sigma Chemical Co.).

Experiment 1

Rats were trained using 45-min sessions on the CRF task for 2 weeks prior to surgery. These rats received intra-accumbens injections of either ascorbate vehicle (n = 9) or 6-OHDA (n = 7) as described above. The rats were then tested for an additional week (45-min sessions, days 3–7 after surgery). After termination of the experiment, these rats were used for tissue assays as described above.

Experiment 2

Rats were trained using 45-min sessions on the CRF task using the same procedure as Experiment 1. After 2 weeks of CRF training the rats were given a 2-day break (corresponding to the 2-day postoperative recovery time in Experiment 1) and then these unoperated rats were exposed either to a continued day of CRF training (n = 5) or to extinction (n = 6). Thus, this test day corresponded to the first test day (day 3 after surgery) in Experiment 1. The extinction procedure used in-

volved firing the feeder when the lever was pressed, but not delivering food [see (28)].

Data Analysis

For Experiment 1, several different analyses of behavioral results were used. Separate analyses were performed on the results of the first behavioral test (day 3 after surgery) because this test was designed to be comparable to the extinction test in Experiment 2. For analysis of the day 3 test results, a factorial analysis of variance (ANOVA) was performed on the number of responses per 15-min interval in the session (2 × 2 ANOVA; DA depletion × 15-min interval). Analysis of simple main effects (15) was used to provide further analyses of the ANOVA data. An additional analysis of the day 3 test results was performed by analyzing the IRT bin distribution. This analysis was done by calculating the percentage of total responses within each of the eight IRT bins. Percentage data were used rather than raw number of IRTs in each bin because the percentage analysis corrects for any differences in the total number of responses in each group, and focusses on the relative distribution of IRTs [see (34)]. Between-group differences in each IRT bin were assessed by using the Mann-Whitney *U*-test. For additional analyses of CRF responding throughout the entire period of postsurgical testing, factorial ANOVA was performed on the total number of responses per day, and on the percentage of total responses within the first 15-min period. The latter measure was analyzed because a previous study (18) indicated that the major effect of accumbens DA depletion was a reduction in responding during the initial portion of the session. To provide an index of the IRT distribution over several days of testing, analyses also were performed on the percentage of IRTs in the first bin. For Experiment 2, the data were analyzed in the same manner as the day 3 test in Experiment 1. Factorial ANOVA was performed on the number of responses per 15-min interval in the session (2 × 2 ANOVA; extinction condition × 15-min interval). Analysis of simple main effects (15) was used to provide further analyses of the ANOVA data. Analysis of the IRT bin distribution was done by calculating the percentage of total responses within each of the eight IRT bins, and analyzing these data with the Mann-Whitney *U*-test.

RESULTS

Experiment 1

Day 3 test session. Figure 1 shows the mean ± SEM number of CRF responses committed by DA-depleted and control rats on day 3 after surgery during each of the three 15-min periods within the 45-min session. ANOVA revealed that there was a significant overall effect of DA depletion, $F(1, 14) = 6.86$, $p < 0.05$, with DA-depleted rats making fewer responses than control rats. There was a significant effect of within-session period, $F(2, 28) = 43.6$, $p < 0.01$, and a significant DA depletion × test period interaction, $F(2, 28) = 25.1$, $p < 0.01$. Analysis of simple main effects indicated that DA-depleted rats made significantly fewer responses than controls in the first 15-min period, $F(1, 14) = 13.4$, $p < 0.01$. There were no significant differences between DA-depleted and control rats during the 15–30-min period or the 30–45-min period. Although the control rats showed a within-session decline in responding, $F(2, 28) = 76.8$, $p < 0.01$, the DA-depleted rats did not, $F(2, 28) = 1.3$, NS. Figure 2 depicts the IRT bin distributions for control and DA-depleted rats during the day 3 test session. DA-depleted rats showed a significantly

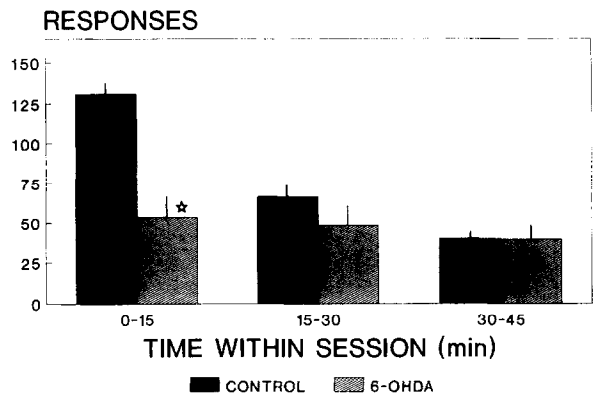

FIG. 1. Mean ± SEM number of lever presses in DA-depleted and control rats during the first test day (day 3 after surgery). Data from all three 15-min periods within the session are shown. *$p < 0.05$, different from controls.

smaller percentage of their IRTs in the IRT bin that corresponded to the highest response rate (IRT = 0–1.5 s; $U = 1$, $p < 0.01$). In the 3.0–4.5-s IRT bin there also was a significant decrease for DA-depleted rats relative to control rats ($U = 6$, $p < 0.01$). In the IRT bin that corresponds to the lowest response rate (i.e., IRT > 12.0 s), the DA-depleted rats showed a significant increase in the percentage of IRTs relative to control rats ($U = 6$, $p < 0.01$).

Overall analyses of postsurgical testing. Figure 3a shows the mean ± SEM number of CRF responses committed by DA-depleted and control rats on days 3–7 after surgery. ANOVA demonstrated that there was no significant overall effect of DA depletion of the total number of CRF responses, $F(1, 14) = 0.1$, NS, but there was a significant effect of test day, $F(4, 56) = 9.1$, $p < 0.01$, and a significant DA depletion × day interaction, $F(4, 56) = 5.54$, $p < 0.05$. Analysis of simple main effects indicated that DA-depleted rats showed a significant increase in responding over days, $F(4, 56) = 12.2$, $p < 0.01$, but control rats did not. Although DA-depleted rats had a significant suppression of total number of lever presses on the first test day, there were no significant differences on any subsequent test day. Figure 3b displays the data

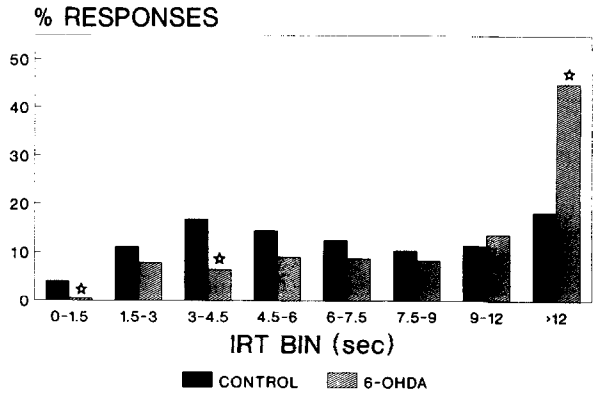

FIG. 2. Mean ± SEM percent of IRTs within each of the eight IRT bins for control and DA-depleted rats. *$p < 0.05$, different from controls.

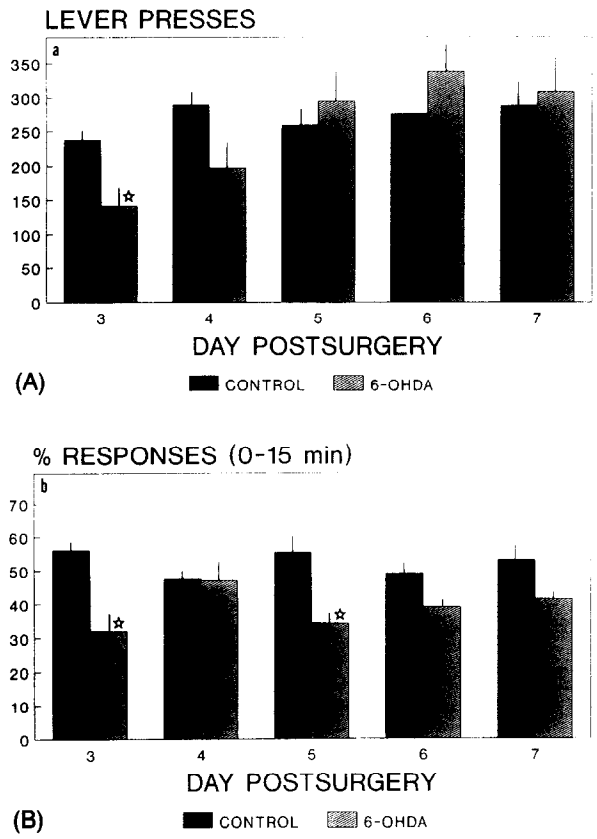

FIG. 3. (a) Mean ± SEM total number of lever presses in DA-depleted and control rats during the postsurgical testing sessions (days 3-7 after surgery). *$p < 0.05$, different from controls. (b) Mean ± SEM percentage of lever presses that were made within the first 15 min of the session in DA-depleted and control rats during the postsurgical testing sessions (days 3-7 after surgery). *$p < 0.05$, different from controls.

on the percentage of total responses that were made within the first 15-min period. There was a significant overall reduction of the percentage of responses emitted during the first 15-min interval in DA-depleted rats, $F(1, 14) = 9.9$, $p < 0.01$, but no significant effect of test day. There was a significant DA depletion × test day interaction, $F(4, 56) = 4.8$, $p < 0.05$, and analysis of simple effects indicated that the DA-depleted group showed a significant increase in this behavioral measure over days, $F(4, 56) = 3.3$, $p < 0.05$, whereas the control rats did not. On days 3-7 after surgery, DA-depleted rats tended to show relatively fewer responses within the first 15-min period compared to control rats; however, this effect only reached statistical significance on days 3 and 5 after surgery. Analysis of the IRT data indicated that, in addition to the effects reported for the day 3 test, DA-depleted rats had a significantly smaller percentage of their IRTs in the 0-1.5-s bin on days 4 and 5 after surgery (day 4: control mean = 6.2%, DA-depleted mean = 2.7%, $U = 13$, $p < 0.05$; day 5: control mean = 2.6%, DA-depleted mean = 0.6%, $U = 12$, $p < 0.05$). Thereafter, there were no significant group differences.

Neurochemical results. HPLC analysis of tissue samples demonstrated that 6-OHDA injection depleted DA in nucleus accumbens but not prefrontal cortex or neostriaum. The mean ± SEM DA contents (in ng/mg wet tissue) of the tissue samples were as follows: control prefrontal cortex 0.12 ± 0.013, 6-OHDA prefrontal cortex 0.09 ± 0.013, $t(14) = 1.52$, NS; control accumbens 6.8 ± 0.35, 6-OHDA accumbens 2.5 ± 0.27, $t(14) = 9.23$, $p < 0.001$; control striatum 10.1 ± 0.69, 6-OHDA striatum 8.52 ± 0.53, $t(14) = 1.7$, NS. DA levels in the nucleus accumbens were significantly correlated with the number of lever pressing responses made during the day 3 test session, $r(5) = 0.81$, $p < 0.05$. Consistent with this significant correlation, the three rats with the lowest levels of accumbens DA (mean = 1.8 ng DA/mg tissue) also made relatively few responses during the day 3 test session (mean = 55.0 responses). Nevertheless, all of these rats recovered very rapidly in terms of the total number of responses, and during the day 4 test session showed a dramatic increase in responding relative to the previous day (mean = 217.3 responses).

Experiment 2

Figure 4 shows the mean ± SEM number of CRF responses emitted by control rats and rats exposed to the extinction procedure during each of the three 15-min periods within the 45-min session. ANOVA revealed that there was a significant overall effect of extinction on lever pressing, $F(1, 9) = 147.1$, $p < 0.001$. There was a significant effect of within-session period, $F(2, 18) = 14.7$, $p < 0.01$, and a significant extinction × test period interaction, $F(2, 18) = 4.3$, $p < 0.05$. Analysis of simple main effects indicated that rats exposed to extinction made significantly fewer responses than controls in the 0-15-min period, $F(1, 9) = 5.2$, $p < 0.05$, the 15-30-min period, $F(1, 9) = 21.6$, $p < 0.01$, and the 30-45-min period, $F(1, 9) = 15.2$, $p < 0.01$. Figure 5 depicts the IRT bin distributions for control and extinction-treated rats. Rats exposed to extinction showed a significantly higher percentage of their IRTs in the IRT bin that corresponded to the highest response rate (IRT = 0-1.5 s; $U = 1$, $p < 0.01$). There were significant decreases in the percentage of IRTs emitted by extinction-treated rats relative to control rats in the 1.5-3.0-s bin ($U = 1$, $p < 0.01$), the 3.0-4.5-s IRT bin ($U = 0$, $p < 0.01$), and the 4.5-6.0-s bin ($U = 0$, $p < 0.01$). In the IRT bin that corresponds to the lowest response rate (i.e., IRT > 12.0 s), the rats exposed to extinction showed a significant increase in the percentage of IRTs emitted relative to control rats ($U = 0$, $p < 0.01$).

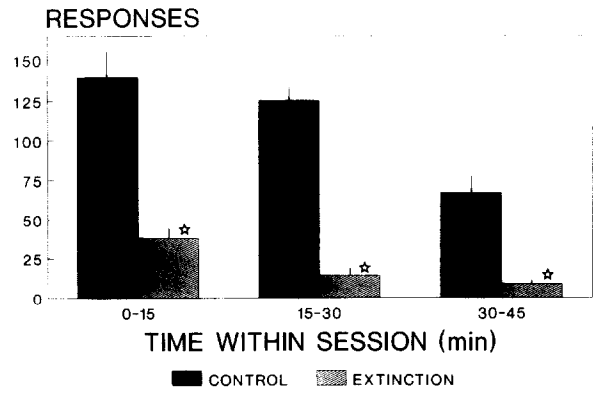

FIG. 4. Mean ± SEM number of lever pressess in control rats and rats exposed to extinction. Data from all three 15-min periods within the session are shown. *$p < 0.05$, different from controls.

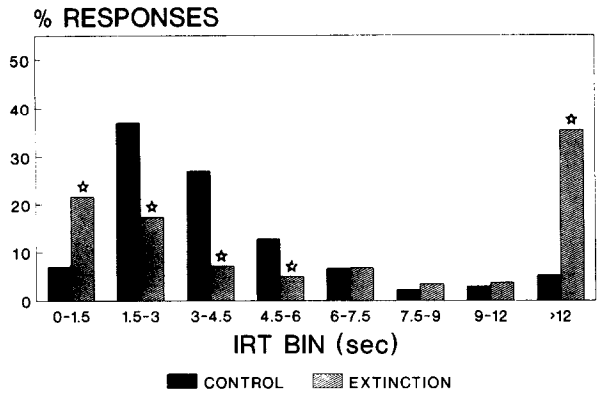

FIG. 5. Mean ± SEM percent of IRTs within each of the eight IRT bins for control rats and rats exposed to extinction. *$p < 0.05$, different from controls.

DISCUSSION

Experiment 1 demonstrated that accumbens DA depletions produced only a slight effect on CRF responding, which was most evident on the first test day (day 3 after surgery). During the day 3 test, rats with accumbens DA depletions showed a reduction in responding during the first 15-min period within the test session, and no significant effects during the 15–30-min or the 30–45-min periods. These results are very similar to a previous report, in which accumbens DA depletions were shown to produce an initial reduction in CRF responding (18). In a recent study of the effects of 6-OHDA injections on fixed ratio 5 (FR5) responding, it was also observed that accumbens DA depletions decreased responding during the first 10 min of a 30-min session, but failed to significantly affect responding during the last 20 min of the session (35). Thus, three separate studies have shown that the major effect of nucleus accumbens DA depletions is to produce an initial slowing of response rate rather than a progressive decline in responding. In addition to these effects upon the initial rate of responding, the present results demonstrated that nucleus accumbens DA depletions produced a slowing of the local rate of responding as measured by the IRT distribution. Rats with accumbens DA depletions showed a significant reduction in the percentage of IRTs in the range of 0–1.5 s. This corresponds to a response rate of greater than 40 responses per minute. Moreover, accumbens DA depletions resulted in a significant increase in the percentage of IRTs in the range of > 12.0 s, which represents a local rate of < 5.0 responses per minute. Thus, the major effect of accumbens DA depletions was a slowing in the local rate of responding. In a previous study of FR5 responding it also was demonstrated that nucleus accumbens DA depletions produced a slowing of the local response rate (35).

In Experiment 1, there was a rapid recovery from the effects of nucleus accumbens DA depletions on CRF responding. This rapid recovery after nucleus accumbens DA depletions has been reported elsewhere (18,19,35), and is generally consistent with the literature on recovery of function after large forebrain DA depletions (41,50). Evidence indicates that the neurochemical mechanisms underlying this recovery process include postsynaptic receptor supersensitivity, a loss of presynaptic uptake sites, and increases in the activity of the remaining DA neurons (1,50,51). In the present study, the ability to show normal levels of total number of responses recovered by the fourth day after surgery. By the sixth day after surgery, DA-depleted rats had recovered in terms of their deficits in initial response rate and local response rate. In one study that used similar lesion methods to those employed in the present study, it was observed the rats with accumbens DA depletions had deficits in the motor activity induced by periodic food presentation, and these deficits were only evident on days 3–7 after surgery (19). A previous study of CRF responding (18) involved the use of pargyline and desipramine to enhance the magnitude of the DA depletion, and in that study it was also observed that total number of responses had recovered by day 4 after surgery. The only major difference between the effects of 89% DA depletions (18) and 64% DA depletions (present study) was that the deficit in initial responding persisted longer in rats with 89% DA depletions (18). The rate of recovery after accumbens DA depletions may depend upon the behavioral task employed as well as the magnitude of the DA depletion. Nucleus accumbens DA depletions have been shown to produce more persistent effects on lever pressing avoidance responding (21), and on instrumental tasks that involve cost/benefit procedures (6). Although gross indices of responding had recovered by the second week after surgery in rats with accumbens DA depletions tested on a FR5 schedule, it was also noted that there were alterations in the IRT distribution that were evident for 3 weeks after surgery (35). This is possibly due to the fact that the FR5 schedule generates a much higher local rate of responding (e.g., > 50% of IRTs faster than 0.5 s) than the CRF schedule. In summary, the present results are consistent with previous reports indicating that accumbens DA depletions produce a deficit in lever pressing that is relatively mild, and that gross indices of responding such as total number of responses recover relatively rapidly after surgery (18,27,35).

Systemic administration of DA antagonists to rats responding on CRF schedules has been reported to result in a progressive within-session decline in responding that was thought to resemble extinction (45–47). In Experiment 2, it was observed that extinction produced effects that were quite different from the effects of accumbens DA depletions. Although DA-depleted rats showed decreased responding relative to control rats only in the first 15-min period, rats exposed to extinction differed substantially from control rats throughout the 45-min test session. Rats with accumbens DA depletions showed decreases in the relative proportion of IRTs faster than 1.5 s. In contrast, rats exposed to extinction showed increases in the relative proportion of IRTs faster than once every 1.5 s, which may in part be due to the activating effects of nonreinforcement as well as the fact that reinforcement pellets were not being consumed. Thus, extinction produced a "bursting" pattern in the IRT distribution that was not shown by DA-depleted rats. In summary, the present results do not support the notion that accumbens DA depletion produces an effect that could be labelled as "extinction-like." In fact, a number of studies also have demonstrated a lack of equivalence between the effects of DA antagonists or accumbens DA depletions and the effects of extinction [(2,8,9,11,12,17,18,25,28, 39,42,43), see reviews in (29,32,33)]. Recently, it was demonstrated that intra-accumbens injections of the DA antagonist *cis*-flupenthixol failed to produce an extinction-like decline in responding on a variable-interval schedule, and instead produced a suppression of responding that resembled the pattern shown in the present study (3). These reports, coupled with the results of Experiments 1 and 2 above, fail to support the hypothesis that accumbens DA directly mediates the basic process of food reinforcement.

In conclusion, the present results indicate that moderate depletions of nucleus accumbens DA reduce the initial response rate and the maximum local response rate. These results demonstrate that one of the major effects of nucleus accumbens DA depletions is motor slowing. Yet despite the evidence indicating that nucleus accumbens DA is involved in aspects of motor function, such as locomotion (16,19,20,39, 44), the precise relation between accumbens DA activity and motor output is somewhat complex. Electrophysiological studies in monkeys indicate that during lever pressing the activity of most ventral tegmental DA neurons is not closely linked to the phasic motor output (23,37). Thus, it seems as though dopaminergic activity in nucleus accumbens does not directly mediate the motor responses involved in lever pressing. Rather, nucleus accumbens DA appears to act by modulating aspects of motor function such as response initiation, local response rate, or responsiveness to stimuli (18,19,32). This modulatory influence of accumbens DA over motor output can be considered as a higher-order motor process that is involved in aspects of motivation such as behavioral activation (18,19,28-36).

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REFERENCES

1. Altar, C. A.; Marien, M. R.; Marshall, J. F. Time course adaptations in dopamine biosynthesis, metabolism, and release following nigrostriatal lesions: Implications for behavioral recovery from brain injury. J. Neurochem. 48:390-399; 1987.
2. Asin, K.E.; Fibiger, H.C. Force requirements in lever-pressing and responding after haloperidol. Pharmacol. Biochem. Behav. 20:323-326; 1984.
3. Beninger, R. J.; Ranaldi, R. Microinjections of flupenthixol into the caudate-putamen but not the nucleus accumbens, amygdala or frontal cortex of rats produce intra-session declines in food-rewarded operant responding. Behav. Brain Res. 55:203-212; 1993.
4. Blackburn, J. R.; Phillips, A. G.; Jakubovic, A.; Fibiger, H.C. Dopamine and preparatory behavior: II. A neurochemical analysis. Behav. Neurosci. 103:15-23; 1989.
5. Cador, M.; Taylor, J. R.; Robbins, T. W. Potentiation of the effects of reward-related stimuli by dopaminergic-dependent mechanisms in the nucleus accumbens. Psychopharmacology (Berlin) 104:377-385; 1991.
6. Cousins, M. S.; Sokolowski, J. D.; Salamone, J. D. Different effects of nucleus accumbens and ventrolateral striatal dopamine depletions on instrumental response selection in the rat. Pharmacol. Biochem. Behav. 46:943-951; 1993.
7. Di Chiara, G.; Imperato, A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc. Natl. Acad. Sci. USA 85: 5274-5278; 1988.
8. Ettenberg, A.; Carlisle, H. J. Neuroleptic-induced deficits in operant behavior for temperature reinforcement. Pharmacol. Biochem. Behav. 22:761-767; 1985.
9. Evenden, J. L.; Robbins, T. W. Dissociable effects of d-amphetamine, chlordiazepoxide and alpha-flupenthixol on choice and rate measures of reinforcement in the rat. Psychopharmacology (Berlin) 79:180-186; 1983.
10. Everitt, B. J.; Cador, M.; Robbins, T. W. Interactions between the amygdala and ventral striatum in stimulus-reward association: Studies using a second-order schedule of sexual reinforcement. Neuroscience 30:63-75; 1989.
11. Faustman, W. O.; Fowler, S. C. Use of operant response duration to distinguish between the effects of haloperidol and non-reward. Pharmacol. Biochem. Behav. 15:327-329; 1981.
12. Faustman, W. O.; Fowler, S. C. An examination of methodological refinements, clozapine and fluphenazine in the anhedonia paradigm. Pharmacol. Biochem. Behav. 17:987-993; 1982.
13. Hernandez, L.; Hoebel, B. G. Food reward and cocaine increase extracellular dopamine in the nucleus accumbens as measured by microdialysis. Life Sci. 42:1705-1712; 1988.
14. Kelley, A. E.; Stinus, L. Disappearance of hoarding behavior after 6-hydroxydopamine lesions of the mesolimbic dopamine neurons and its reinstatement with L-DOPA. Behav. Neurosci. 99:531-5435; 1985.
15. Keppel, G. Design and analysis: A researchers handbook. Englewood Cliffs, NJ: Prentice Hall; 1982.
16. Koob, G. F.; Riley, S. J.; Smith, S. C.; Robbins, T. W. Effects of 6-hydroxydopamine lesions of the nucleus accumbens septi and olfactory tubercle on feeding, locomotor activity, and amphetamine anorexia in the rat. J. Comp. Physiol. Psychol. 92:917-927; 1978.
17. Mason, S. T.; Beninger, R. J.; Fibiger, H. C.; Phillips, A. G. Pimozide-induced suppression of responding: Evidence against a lack of food reward. Pharmacol. Biochem. Behav. 12:917-923; 1980.
18. McCullough, L. D.; Cousins, M. S.; Salamone, J. D. The role of nucleus accumbens dopamine in responding on a continuous reinforcement operant schedule: A neurochemical and behavioral study. Pharmacol. Biochem. Behav. 46:581-586; 1993.
19. McCullough, L. D.; Salamone, J. D. Involvement of nucleus accumbens dopamine in the motor activity induced by periodic food presentation: A microdialysis and behavioral study. Brain Res. 592:29-36; 1992.
20. McCullough, L. D.; Salamone, J. D. Increases in extracellular dopamine levels and locomotor activity after direct infusion of phencyclidine into the nucleus accumbens. Brain Res. 577:1-9; 1992.
21. McCullough, L. D.; Sokolowski, J. D.; Salamone, J. D. A neurochemical and behavioral investigation of the involvement of nucleus accumbens dopamine in instrumental avoidance. Neuroscience 52:919-925; 1993.
22. Mittleman, G.; Whishaw, I. Q.; Jonds, G. H.; Koch, M.; Robbins, T. W. Cortical, hippocampal, and striatal mediation of schedule-induced behaviors. Behav. Neurosci. 104:399-409; 1990.
23. Nishino, H.; Ono, T.; Muramoto, K.; Fukuda, M.; Sasaki, K. Neuronal activity in the ventral tegmental area (VTA) during motivated bar press feeding in the monkey. Brain Res. 413:302-313; 1987.
24. Pfaus, J. G.; Phillips, A. G. Role of dopamine in anticipatory and consummatory aspects of sexual behavior in the male rat. Behav. Neurosci. 105:727-743; 1991.
25. Phillips, A. G.; Fibiger, H. C. Decreased resistance to extinction after haloperidol: Implications for the role of dopamine in reinforcement. Pharmacol. Biochem. Behav. 10:751-761; 1979.
26. Robbins, T. W.; Koob, G. F. Selective disruption of displacement behaviour by lesions of the mesolimbic dopamine system. Nature 285:409-412; 1980.
27. Roberts, D. C. S.; Corcoran, M. E.; Fibiger, H. C. On the role of ascending catecholaminergic systems in intravenous self-administration of cocaine. Pharmacol. Biochem. Behav. 6:615-620; 1977.
28. Salamone, J. D. Different effects of haloperidol and extinction on instrumental behaviors. Psychopharmacology (Berlin) 88:18-23; 1986.
29. Salamone, J. D. The actions of neuroleptic drugs on appetitive instrumental behaviors. In: Iversen, L. L.; Iversen, S. D.; Snyder, S. H., eds. Handbook of psychopharmacology. New York: Plenum Press; 1987:575-608.
30. Salamone, J. D. Dopaminergic involvement in activational aspects of motivation: Effects of haloperidol on schedule-induced

activity, feeding and foraging in rats. Psychobiology 16:196-206; 1988.
31. Salamone, J. D. Behavioral pharmacology of dopamine systems: A new synthesis. In: Willner, P.; Scheel-Kruger, J., eds. The mesolimbic dopamine system: From motivation to action. Cambridge, England: Cambridge University Press; 1991:599-613.
32. Salamone, J. D. Complex motor and sensorimotor functions of accumbens and striatal dopamine: Involvement in instrumental behavior processes. Psychopharmacology (Berlin) 107:160-174; 1992.
33. Salamone, J. D. The involvement of nucleus accumbens dopamine in appetitive and aversive motivation. Behav. Brain Res. 61: 117-133; 1994.
34. Salamone, J. D.; Cousins, M. S.; McCullough, L. D.; Carriero, D. L.; Berkowitz, R. L. Nucleus accumbens dopamine release increases during instrumental lever pressing for food but not food consumption. Pharmacol. Biochem. Behav. 49(1):25-31; 1994.
35. Salamone, J. D.; Kurth, P. A.; McCullough, L. D.; Sokolowski, J. D.; Cousins, M. S. The role of brain dopamine in response initiation: Effects of haloperidol and regionally specific dopamine depletions on the local rate of instrumental responding. Brain Res. 628:218-226; 1993.
36. Salamone, J. D.; Steinpreis, R. E.; McCullough, L. D.; Smith, P.; Grebel, D.; Mahan, K. Haloperidol and nucleus accumbens dopamine depletion suppress lever pressing for food but increase free food consumption in a novel food-choice procedure. Psychopharmacology (Berlin) 104:515-521; 1991.
37. Schultz, W.; Apicella, P.; Ljungberg, T. Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task. J. Neurosci. 13: 900-913; 1993.
38. Sokolowski, J. D.; Salamone, J. D. Effects of dopamine depletions in the medial prefrontal cortex on DRL performance and motor activity in the rat. Brain Res. 642:20-28; 1994.
39. Spivak, K. J.; Amit, Z. Effects of pimozide on appetitive behavior and locomotor activity: Dissimilarity of effects when compared to extinction. Physiol. Behav. 36:457-463; 1986.
40. Steinpreis, R. E.; Salamone, J. D. The role of nucleus accumbens dopamine in the neurochemical and behavioral effects of phencyclidine. Brain Res. 612:263-270; 1993.
41. Stricker, E. M.; Zigmond, M. J. Recovery of function after damage to central catecholamine-containing neurons: A neurochemical model for the lateral hypothalamic syndrome. In: Sprague, J. M., ed. Progress in psychobiology and physiological psychology. New York: Academic Press; 1976:121-173.
42. Tombaugh, T. N.; Anisman, H.; Tombaugh, J. Extinction and dopamine receptor blockade after intermittent reinforcement training: Failure to observe functional equivalence. Psychopharmacology (Berlin) 70:19-28; 1980.
43. Willner, P.; Chawala, K.; Sampson, D.; Sophokleous, S.; Muscat, R. Tests of functional equivalence between pimozide pretreatment, extinction and free feeding. Psychopharmacology (Berlin) 95:423-426; 1988.
44. Winn, P.; Robbins, T. W. Comparative effects of infusions of 6-hydroxydopamine into nucleus accumbens and anterolateral hypothalamus induced by 6-hydroxydopamine on the response to dopamine agonists, body weight, locomotor activity and measures of exploration in the rat. Neuropharmacology 24:25-31; 1985.
45. Wise, R. A. Neuroleptics and operant behavior: The anhedonia hypothesis. Behav. Brain Sci. 5:39-87; 1982.
46. Wise, R. A.; Spindler, J.; De Witt, H.; Gerber, G. J. Neuroleptic-induced "anhedonia" in rats: Pimozide blocks reward quality of food. Science 201:262-264; 1978.
47. Wise, R. A.; Spindler, J.; Legult, L. Major attenuation of food reward with performance-sparing doses of pimozide in the rat. Can. J. Psychol. 32:77-85; 1978.
48. Zahm, D. S.; Brog, J. S. On the significance of subterritories in the "accumbens" part of the rat ventral striatum. Neuroscience 50:751-767; 1992.
49. Zahm, D. S.; Heimer, L. Two transpallidal pathways originating in the rat nucleus accumbens. J. Comp. Neurol. 302:437-446; 1990.
50. Zigmond, M. J.; Stricker, E. M. Parkinson's disease: Studies with an animal model. Life Sci. 35:5-18; 1984.
51. Zigmond, M. J.; Stricker, E. M. Adaptive properties of monoaminergic neurons. Handbook Neurochem. 9:87-102; 1985.