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The Role of Nucleus Accumbens Dopamine in Responding on a Continuous Reinforcement Operant Schedule: A Neurochemical and Behavioral Study

L. D. McCULLOUGH, M. S. COUSINS AND J. D. SALAMONE[1]

Department of Psychology, University of Connecticut, Storrs, CT 06269-1020

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McCULLOUGH, L. D., M. S. COUSINS AND J. D. SALAMONE. *The role of nucleus accumbens dopamine in responding on a continuous reinforcement operant schedule: A neurochemical and behavioral study.* PHARMACOL BIOCHEM BEHAV **46**(3) 581–586, 1993.—Two experiments were undertaken to investigate the role of nucleus accumbens dopamine (DA) in intrumental lever pressing on a continuous reinforcement (CRF) schedule. Rats trained to press a lever for food reinforcement on a CRF schedule, and food-deprived control rats, were implanted with dialysis probes in the nucleus accumbens. The day after implantation, rats were tested and dialysis samples were assayed for DA and the DA metabolite 3,4-dihydroxyphenylacetic acid (DOPAC). Performance of the lever-pressing task resulted in significant increases in extracellular levels of DA and DOPAC relative to control rats. The increases in extracellular DA were significantly correlated (r = 0.92) with the number of lever press responses committed. In the second 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. 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 in the session. This initial slowing of response rate was present across all 5 test days. These results indicate that DA release and metabolism increases in rats performing on a CRF schedule, and that DA depletion produces a slowing of initial response rate.

Nucleus accumbens Dopamine Motivation Operant behavior Microdialysis Behavioral activation

ALTHOUGH considerable evidence indicates that dopamine (DA) is involved in the performance of appetitively motivated behavior, the precise behavioral functions performed by DA systems remain uncertain. There is general agreement that systemic administration of DA antagonists impairs various instrumental responses that are supported by positive reinforcers [for reviews see (27,29,30,40)]. Because interference with DA systems can have such pronounced effects on positively reinforced responses, it has been suggested that DA systems are important for mediating the hedonic effects of rewarding stimuli (40–42). DA in nucleus accumbens has received particular emphasis in regards to the hypothesized involvement of DA in appetitive motivation (6,12). Yet despite the evidence linking accumbens DA with reinforcement processes, there have been very few studies focussing on the role of accumbens DA in responding on a continuous reinforcement (CRF) schedule for food reinforcement. It is important to examine the role of accumbens DA in the performance of CRF responding, because this schedule represents a fundamental reinforcement condition in which there is primary positive reinforcement that involves a natural reinforcer. It was observed that rats pressing a lever to receive food on a CRF schedule showed increases in extracellular DA in nucleus accumbens as measured by in vivo microdialysis (12). In that experiment, no correlations between neurochemical and behavioral data were reported, and it was not clear how the increases in DA release were related to behavioral performance. Thus, the first experiment of the present series involved implantation of dialysis probes into the nucleus accumbens of rats trained to press a lever on a CRF schedule for food reinforcement, to determine how behavioral performance was related to changes in DA release or metabolism in

[1] To whom requests for reprints should be addressed.

nucleus accumbens. Another method that is used to investigate the behavioral functions of accumbens DA is the use of the neurotoxic agent, 6-hydroxydopamine (6-OHDA), to produce a local depletion of DA in the nucleus accumbens. Although the behavioral effects of accumbens DA depletion have been studied using a wide variety of behavioral tasks (13,15,17,19,20,25,34,37), the effects of accumbens DA depletion on CRF responding have not been specifically characterized. For the second experiment, DA in nucleus accumbens was depleted by local injections of 6-OHDA to assess the effects of DA depletion on CRF performance.

METHOD

Animals

A total of 37 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, with a 12L : 12D cycle (lights on 0700).

Behavioral Procedures

For all experiments, testing was performed in operant chambers (28 × 23 × 23cm). All 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 Bioserve pellets (Frenchtown, NJ), and small pieces of lab chow were placed 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 2 weeks of training on the CRF schedule before the experiments began. Typically, rats were emitting 200 or more lever press responses by the end of the last training session. Rats being used for Experiment 1 were trained to press the lever in Plexiglas chambers that were kept in small test rooms. When the CRF schedule was in operation, the room lights were turned off, but small house lights in the chamber were left on. The room lights were turned on again when the test session was over, but the rats were left in the chambers with the room lights on and no food available. This procedure was used to train the rats for the dialysis tests, during which the CRF schedule would only be available for one 45-min session during the test day. In Experiment 2 a computer program was used to analyze the pattern of responding on the CRF task 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.

Dialysis Probe Construction

The exposed surface of the dialysis probe consisted of a loop of 200-μm diameter dialysis tubing (15,000 M.W. cutoff) with a strand of 0.002-in. diameter stainless steel wire threaded through the inside of the tubing for structural support. Both ends of the dialysis tubing were glued to polyethylene tubing (PE-10), and the dialysis probe was formed into a very tight loop such that the two sides of the dialysis fiber loop were right next to each other. The active surface area of the dialysis probe was 1.5 mm in length. Super glue was used to support the dialysis fiber and PE tubing, and to attach the PE tubing to an 18-ga stainless steel casing that was used for overall support of the probe. Presurgical recovery tests using probes identical to those used in the present study have shown that there is a 13–18% recovery of DA and DOPAC in beakers at room temperature with a flow rate of 1.5 μl/min.

Dialysis Probe Implantation

Dialysis probes were implanted in the nucleus accumbens (AP 2.8 mm from bregma, ML 1.4 mm, V −7.8 mm from skull, with the incisor bar elevated 5.0 mm above interaural line). The entire assembly was anchored to the skull using machine screws and cranioplastic cement. The two strands of PE-10 from the probe were fed through a metal tether and connected to a fluid swivel (Harvard Apparatus) at one end and an open sample collection tube at the other end. The probe was perfused with artificial CSF at 1.5 μl/min by a Hamilton syringe driven with a Harvard Apparatus syringe pump. The CSF contained 147.2 mM NaCl, 2.3 mM $CaCl_2$, and 4.0 mM KCl. Rats were placed in the locomotor activity chamber and allowed 1 day to recover before the behavioral test session. Baseline DA levels on the day of the test session were typically in the range of 15–30 pg DA per 60 μl of dialysate. Thus, our estimation of the baseline extracellular levels of DA was approximately 10 nM.

Neurochemical Analysis of DA and DOPAC

The dialysis samples from Experiment 1 and the tissue samples from Experiment 2 were analyzed for their neurochemical content using a high performance liquid chromatography (HPLC) system that 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 and DOPAC were assayed before, during, and after the samples (Sigma Chemical Co.).

Accumbens DA Depletion by Injection of 6-OHDA

In Experiment 2, 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. A total of 10.0 μg of the free base of 6-OHDA dissolved in 0.1% ascorbic acid was injected per side (2.0 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 2.0 μl of the 0.1% ascorbate solution at the same site as 6-OHDA-treated rats. All rats were injected with 50.0 mg/kg pargyline and 15.0 mg/kg desipramine 30 min prior to surgery.

Histology

After Experiment 1, rats were anesthetized with sodium pentobarbital and perfused with saline and 10% formalin. After perfusion, the dialysis probes were removed, and the brains were removed from the skull and stored in a formalin solution. Brains were cut in coronal sections (50 μm) in the vicinity of the dialysis probe, were mounted on microscope slides, and stained with cresyl violet. This histological analysis verified that all the probe placements were within the nucleus accumbens.

Dissections for Tissue Assays

After Experiment 2, rats were decapitated and their brains were removed and frozen. Coronal sections 1.0 mm thick were cut through the brain, and samples of 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. The supernatant (10-μl samples from each tube) was used for HPLC analyses, as described above.

Experiment 1

Previously trained rats were implanted with dialysis probes and tested the next day. Dialysis samples and behavioral data were collected in 45-min periods. A neurochemical and behavioral baseline was established over 4–5 samples, during which the room lights were on and food was not available. The rats were then exposed to one of the two following treatments for a single 45-min period: CRF responding (as described above) or a food-deprived control procedure. During the 45-min period of the behavioral treatment for both groups, the lights in the test room were dimmed as described above. Three more samples were collected after behavioral treatment. After the experiment, rats were perfused and their brains were histologically examined, as described above.

Experiment 2

Rats were trained for 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 = 8) 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.

Data Analysis

In Experiment 1, the mean baseline levels for DA and DOPAC were calculated for the last two samples prior to the behavioral session, and all data for these compounds were recalculated as percent of the pretreatment mean. The Student's t-test was used to test for differences between control and CRF rats during the period of the behavioral test session. Factorial ANOVA with repeated measures on the sample time variable was performed on the data from the samples obtained after behavioral treatment. The Pearson product-moment correlation coefficient was used to establish relations between neurochemical and behavioral data. The data from Experiment 2 were log transformed and analyzed by a three-way factorial ANOVA (group × day × 15-min interval). Analysis of simple main effects (14) was used to provide further analyses of the ANOVA data.

RESULTS

Experiment 1

Lever pressing on a CRF schedule for food reinforcement was accompanied by substantial increases in extracellular levels of DA and DOPAC. Figure 1 depicts the effects of the behavioral treatments on DA content of dialysis perfusates. There was a significant difference in DA content between rats performing on the CRF schedule and control rats in the sample collected during behavioral performance, $t(18) = 3.61$, $p < 0.01$. The mean ± SEM number of lever presses in the CRF group was 139.5 ± 23.7. There was a significant correlation ($r = 0.92$, $p < 0.05$) between the total number of lever press responses and the increase in extracellular DA obtained during the period of instrumental performance (see Fig. 2). After the behavioral test period, extracellular DA levels returned to baseline levels and there were no significant differences between the CRF group and the control group. Figure 3

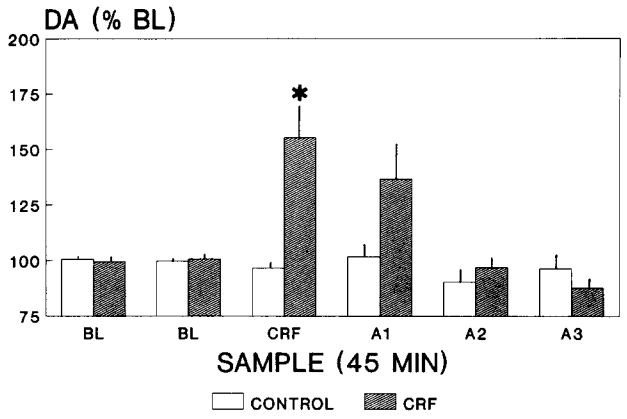

FIG. 1. Mean ± SEM DA content (expressed as percent of baseline) in accumbens dialysis perfusates for rats performing on the CRF task and for control rats. Data are from the last two baseline samples (BL), the sample obtained during the behavioral treatment (CRF), and the three samples obtained after treatment (A1–3). *$p < 0.05$.

shows the effects of CRF performance on DOPAC content of dialysis perfusates. There was a significant difference between rats performing on the CRF schedule and control rats in the sample collected during behavioral performance, $t(18) = 2.22$, $p < 0.05$. After the behavioral test period, extracellular DOPAC levels returned to baseline levels and there were no significant differences between the CRF group and the control group.

Experiment 2

Figure 4 shows the mean ± SEM number of CRF responses committed by DA-depleted and control rats on days 3–7 after surgery during each of the three 15-min periods. ANOVA demonstrated that there was a significant group × day interaction, $F(4, 60) = 5.15$, $p < 0.05$. Analysis of simple effects demonstrated that DA-depleted rats had a significant suppression of total number of lever presses only on the first test day, which was day 3 after surgery, $F(1, 35) = 75.3$, $p < 0.001$. The group difference in total number of lever presses approached significance on the second test day, $F(1, 35) = 3.84$, $p < 0.1$, and there were no significant differ-

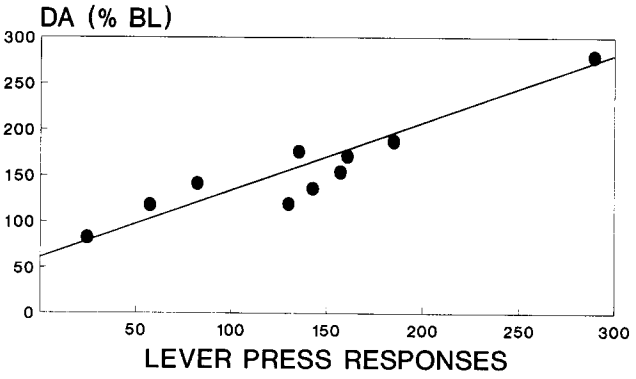

FIG. 2. Scatterplot showing the relation between number of lever pressing responses and DA [as percent of baseline (BL)] in the dialysis sample collected during behavioral performance.

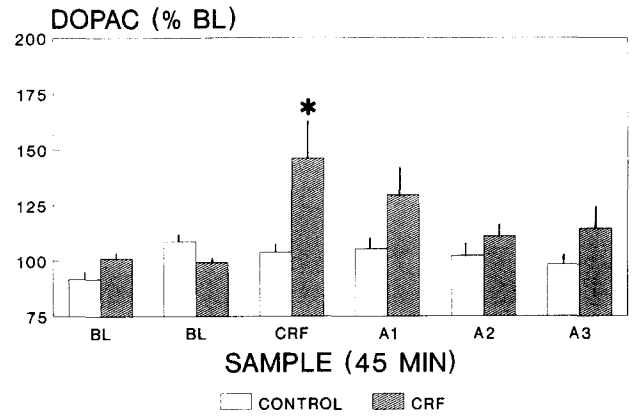

FIG. 3. Mean ± SEM DOPAC content (expressed as percent of baseline) in accumbens dialysis perfusates for rats performing on the CRF task and for control rats. Data are from the last two baseline samples, the sample obtained during the behavioral treatment, and the three samples obtained after treatment. *$p < 0.05$.

ences in total number of responses on any other test day. There also was a significant group × time interval interaction, $F(2, 30) = 13.84$, $p < 0.01$, indicating that rats with accumbens DA depletions showed a different pattern of responding within the session compared to control rats. Analysis of simple main effects demonstrated that control rats showed a significant overall decline in responding within the test session, $F(2, 30) = 108.2$, $p < 0.001$, but rats with accumbens DA depletions did not, $F(2, 30) = 2.66$, NS. In addition, there were significant overall differences between control and DA-depleted rats within the first 15-min period, $F(1, 16) = 34.7$, $p < 0.001$, but not during the second or last 15-min period. There was not a significant three-way interaction.

HPLC analysis of tissue samples demonstrated that 6-OHDA injection depleted accumbens but not striatal DA. The mean ± SEM DA contents (in ng/mg wet tissue) of the tissue samples were as follows: control accumbens, 7.6 ± 0.7; 6-OHDA accumbens, 0.83 ± 0.1, $t(15) = 9.56$, $p < 0.001$; control striatum, 15.1 ± 1.7, 6-OHDA striatum, 13.7 ± 1.2 ($t = 0.7$, NS).

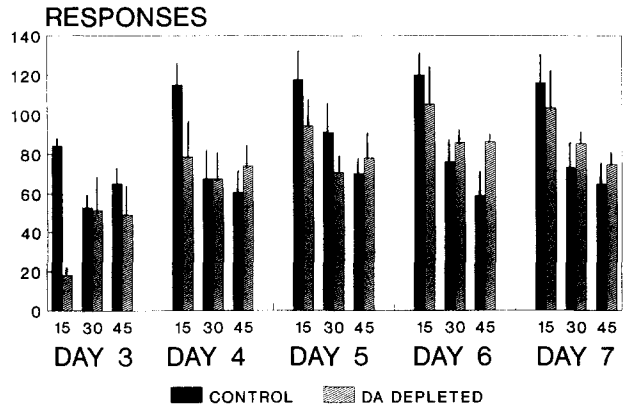

FIG. 4. Mean ± SEM total lever pressess in DA-depleted and control rats during the 5 test days (days 3–7 after surgery). Data from all three 15-min periods are shown (15 = 0–15 min, 30 = 15–30 min, 45 = 30–45 min).

DISCUSSION

It was previously reported that accumbens DA release increased during CRF responding (12), and several studies have shown that accumbens DA release or metabolism is increased during the performance of appetitive tasks (3,17,23). The present results confirm and extend these earlier reports. In Experiment 1, it was shown that lever pressing on a CRF schedule was accompanied by significant increases in the extracellular levels of DA in nucleus accumbens. DA metabolism, as measured by extracellular levels of DOPAC, also was increased in rats performing on the CRF schedule. The increases in extracellular DA shown during the behavioral test session were highly correlated ($r = 0.92$) with the number of lever presses performed. These data indicate that dopaminergic activity in the nucleus accumbens is closely related to aspects of instrumental responding on the CRF schedule.

Based solely on the present results, it is uncertain if the increases in accumbens DA release that accompany CRF performance resulted from the presentation of large amounts of food, the execution of the lever-pressing response itself, or some other factors. Evidence from our laboratory has demonstrated that DA release in nucleus accumbens does not appear to be closely related in any simple way to the presentation of large quantities of food. Periodic food presentation (one 45-mg food pellet every 45 s) caused substantial increases in accumbens DA release and also induced heightened levels of motor activity (17). In that study, there was a modest but significant correlation between locomotor activity and the increases in DA release (17). Nevertheless, consumption of much larger quantities of food (15–18 g of the same pellets used in the present study) did not result in significant increases in accumbens DA release (17). Thus, evidence indicates that accumbens DA release is not necessarily related to food presentation itself. Yet, it is also true that DA release in nucleus accumbens probably does not directly mediate the motor responses involved in lever pressing. Electrophysiological evidence indicates that the activity of most ventral tegmental neurons that increase during lever pressing is not directly related to the phasic motor output (22). Thus, the relation between accumbens DA release and motor activity is poorly understood, and may be somewhat complex. It has been suggested that DA release in nucleus accumbens may act to modulate aspects of motor functions (e.g., response rate or initiation, or responsiveness to stimuli), but may not directly control motor output (17,30). The modulatory influence of accumbens DA over motor output may represent a higher-order motor function that is closely related to the concept of motivation (30). This suggestion is consistent with the notion that DA in nucleus accumbens is involved in the behavioral activation that occurs in motivationally relevant conditions (17,27–30,34).

Although the present experiment involved aspects of appetitive motivation, considerable evidence indicates that nucleus accumbens DA release does not appear to be selectively responsive to positively reinforcing conditions. Enhanced DA release in nucleus accumbens also accompanies aversive conditions as well as appetitive conditions (1,5,18,19). Lever pressing to avoid shock at response rates that were comparable to those obtained in the present study also led to increases in accumbens DA release and metabolism, and these increases in DA release were significantly correlated with the overall rate

of avoidance responding (19). Administration of anxiogenic drugs, which have aversive properties, has been shown to increase accumbens DA release and metabolism (18). It is reasonable to suggest, from the present results as well as other studies cited above, that nucleus accumbens DA release is increased during a variety of motivationally relevant conditions that include both appetitive and aversive motivation (17–19,30).

Despite the large increases in DA release that occurred during lever-pressing performance, substantial depletions of accumbens DA had only a modest effect on lever-pressing performance. There was a significant suppression of the total number of lever presses on the first test day, which was 3 days after surgery. Subsequent to that first test session, the total number of lever press responses in rats with accumbens DA depletions rapidly recovered to normal levels. Rats typically recover from the effects of DA depletions (17,34,36), although the recovery in the present study was extremely rapid. Other research from our laboratory has shown that the behavioral effects of accumbens DA depletion vary greatly depending upon the particular task employed. Depletion of accumbens DA produced a severe and persistent impairment of lever pressing on an avoidance schedule (18). Motor activity induced by periodic food presentation was impaired by injections of 6-OHDA into the accumbens for 1 week after surgery (17). Yet food intake, feeding rate, and food handling were totally unimpaired by accumbens DA depletion, even during the test that was conducted only 3 days after surgery (33). It is possible that the deficit in total number of responses shown in the present study was relatively modest because the CRF schedule generates only a moderate rate of responding. DA depletions in nucleus accumbens may have a greater effect on tasks that involve more vigorous behavioral output or require a greater amount of effort (21,30), such as ratio schedules of reinforcement. Performance of an instrumental response task that involved lever pressing on a fixed ratio 5 schedule was greatly impaired by accumbens DA depletion (32,34). Also, it is possible that the total number of CRF responses was not substantially impaired by accumbens DA depletion because this schedule involves primary and continous reinforcement. Performance on intermittent schedules of reinforcement (33) or tasks involving secondary reinforcement (4,9,37) might be more greatly affected by accumbens DA depletions. It has been suggested that several factors, including the vigor of the behavioral output, the instrumental or consummatory nature of the response, and reliance on conditioned stimuli may all interact to influence the severity of the impairments produced by accumbens DA depletion (29,30).

As well as showing a modest and transient reduction in the total number of lever presses, DA-depleted rats had deficits in subtle features of instrumental responding. Although DA-depleted rats did not have a deficit in total numbers of responses on days 4–7 after surgery, they continued to respond less than controls within the initial portions of the test session. It appears as though rats with accumbens DA depletion remain directed towards food consumption, yet they have a lower initial response rate, and possibly have a lower maximum rate. Within the 45-min session, rats with accumbens DA depletions could compensate for their lower initial rate of responding by continuing to respond throughout the test session. In most cases, rats with accumbens DA depletions started out responding slower than the control mean in the initial portion of the test session, but faster than the control mean towards the end of the session.

Systemic administration of DA antagonists to rats responding on CRF schedules has been reported to result in near normal responding in the beginning of the test session but declines thereafter (40–42), a pattern that resembles withdrawal of reinforcement (i.e., extinction). The pattern of impairment shown by rats with accumbens DA depletions was markedly different from these reported effects of extinction and DA antagonism on CRF performance. In fact, the relation between DA antagonism and extinction is somewhat complicated, and the suggested similarity between the effects of DA antagonism and extinction has been challenged by some researchers. Numerous experiments using DA antagonists have demonstrated a lack of equivalence between the effects of systemic administration of DA antagonists and the effects of extinction [(2,7,8,10,11,16,24,26,35,38,39), see reviews (27, 30)]. The pattern of effects produced by accumbens DA depletion on CRF performance in the present study suggests that the term "extinction effect" should not be applied.

The present results indicate that lever pressing on a CRF schedule is accompanied by increases in accumbens DA release, and that the increases in accumbens DA release were highly correlated with the number of responses performed. Although performance on the CRF schedule was accompanied by large increases in DA release, the effects of DA depletion on total number of responses were relatively minor. Depletion of DA in nucleus accumbens led to a transient decrease in the total number of responses. These results suggest that there still is not a clear relation between the magnitude of DA release during a particular task and the severity of effects produced by DA depletion on global indices of performance of that same task. Nevertheless, accumbens DA depletion did have subtle effects on the temporal characteristics of instrumental responding, and the main effect of accumbens DA depletion was to decrease response rate within the initial portion of the test session. Taken together, these neurochemical and behavioral data suggest that a major function of DA in nucleus accumbens may be to facilitate the instigation of some forms of instrumental behavior. This function may represent an aspect of motor function that is fundamentally related to motivational processes.

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