Pergamon

Pharmacology Biochemistry and Behavior, Vol. 49, No. 1, pp. 85-91, 1994

0091-3057/94 $6.00 + .00

0091-3057(94)E0094-X

Nucleus Accumbens Dopamine Depletions in Rats Affect Relative Response Allocation in a Novel Cost/Benefit Procedure

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Received 15 December 1993

COUSINS, M. S. AND J. D. SALAMONE. *Nucleus accumbens dopamine depletions in rats affect relative response allocation in a novel cost/benefit procedure.* PHARMACOL BIOCHEM BEHAV **49**(1) 85-91, 1994.—Rats were tested on days 1, 3, and 5 of a 5-day test week in an operant chamber in which they could either lever press on a fixed-ratio 5 (FR5) schedule to obtain food pellets (Bioserve) or approach and consume lab chow that was also available in the chamber (Teklad Premier). Rats typically pressed at high rates to obtain the food pellets and ate little of the lab chow. On days 2 and 4 of each week lab chow was not concurrently available, and rats could only lever press on the FR5 schedule for pellets to obtain food. Dopamine depletions produced by intraaccumbens injections of the neurotoxic agent 6-hydroxydopamine produced a dramatic decrease in lever pressing and increase in chow consumption on days when lab chow was available. Lever pressing was not significantly reduced in dopamine-depleted rats on days when chow was not available, although there was a significant correlation between lever pressing and accumbens dopamine levels. These results suggest that nucleus accumbens dopamine depletions do not produce a general deficit in food motivation. Moreover, accumbens dopamine depletions do not appear to produce severe deficits in fine motor control that impair the execution of individual motor acts involved in lever pressing. Rather, the present results are consistent with the notion that accumbens dopamine sets constraints upon which food-related response is selected in a particular situation, and that these depletions alter the relative allocation of food-related responses.

Nucleus accumbens Dopamine Motivation Instrumental behavior Feeding Reinforcement Behavioral economics

CONSIDERABLE evidence indicates that pharmacological antagonism of brain dopamine (DA) receptors impairs instrumental lever pressing behavior (10,11,33,34,54,57). Typically, this effect has been interpreted by various researchers as reflecting dopaminergic involvement in distinct motor or reinforcement processes. Brain DA systems have been implicated in aspects of motor and sensorimotor function (11,16,24, 45,49,52). It also has been suggested that DA antagonists reduce the rewarding impact of stimuli such as food, water, electrical brain stimulation, and drugs of abuse (54-57). The nucleus accumbens is an important DA terminal area that has been implicated in the control of locomotor activity (21,25, 48,53). In addition, the nucleus accumbens is often suggested as being the brain region in which DA is closely involved in the reinforcement process (8,13).

There are several problems with the hypothesis that nucleus accumbens DA directly mediates the positive reinforcement or appetitve motivation produced by food. Accumbens DA depletions that severely impaired cocaine self-administration had very little effect on food-reinforced lever pressing (32). Extensive depletions of accumbens DA had only a transient effect on food- reinforced responding supported on a continuous (CRF) schedule (26). Nucleus accumbens DA depletions did not produce an extinction-like within-session decline in CRF responding (26). With rats responding on a fixed ratio 5 (FR5) schedule, accumbens DA depletion produced a minor suppression of lever pressing that was only significant during the first week after DA depletion (42). Accumbens DA depletions failed to have any significant effects on food intake, feeding rate, or food handling (43). Injections of the DA antagonist haloperidol directly into the nucleus accumbens failed to have any substantial effects on food intake (2).

Recently, the involvement of accumbens DA in appetitive responding has been studied using cost/benefit procedures, such as concurrent lever pressing/feeding tasks (7,44). In this type of task, rats can select between lever pressing for a more preferred food or consuming a less preferred lab chow that is concurrently available in the operant chamber (44). Under

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these conditions, rats will typically lever press on CRF or FR5 schedules and consume little of the freely available lab chow. Systemic or intraaccumbens haloperidol treatment, or 6-hydroxydopamine (6-OHDA) injections into the nucleus accumbens, produce a dramatic shift in behavior such that lever pressing is reduced but lab chow consumption is increased (7,44). Haloperidol treatment or nucleus accumbens DA depletions produced effects different than those observed with prefeeding (44). Moreover, systemic haloperidol did not alter the preference for pellets over lab chow in a free-feeding preference test (44). In contrast to the decrease in lever pressing and increase in chow consumption produced by accumbens DA depletions, ventrolateral neostriatal DA depletions have been shown to produce profound motor impairments that decrease both lever pressing and chow consumption in the concurrent FR5/feeding task (7), as well as in more conventional procedures that assessed these behaviors independently (16,42, 43). Thus, the effects of nucleus accumbens DA depletions are distinct from those produced by a general reduction of food motivation (i.e., prefeeding) and from profound motor impairment (i.e., ventrolateral striatal DA depletions).

The present study was undertaken to provide an additional behavioral characterization of the effects of nucleus accumbens DA depletions on lever pressing and chow consumption. Based upon previous studies, it is not clear if the shift from lever pressing to consumption of lab chow following nucleus accumbens DA depletions is simply due to a lever pressing deficit that sets an absolute ceiling on the number of responses that can be emitted. A comparison of the effects of DA depletions on FR5 responding when chow was not available (42) with effects of similar depletions on a concurrent FR5/feeding procedure (7) indicates that accumbens DA depletions produced a much greater suppression of FR5 responding when chow was concurrently available. This would suggest that the suppression of lever pressing produced by accumbens DA depletions in the FR5/feeding task is not due simply to a motor execution deficit that sets an absolute limit on lever pressing rate. However, such a conclusion is difficult based solely on comparisons between two separate studies involving different groups of animals. In the present study, the effects of intraaccumbens 6-OHDA injections were compared on two alternating procedures. On days 1, 3, and 5 of a 5-day test week the rats were tested on the concurrent FR5/feeding task; on days 2 and 4 of the 5-day test week the rats could only obtain food by lever pressing. This procedure allowed for direct comparisons between the effects of accumbens DA depletions on lever pressing per se vs. effects upon lever pressing in the choice procedure when chow was concurrently available.

METHOD

Animals

The subjects for this experiment were male Sprague-Dawley rats (Harlan Sprague-Dawley, Indianapolis, IN). They were individually housed in a colony at 23°C on a 12 L : 12 D cycle (lights on 0700 h). Water was available ad lib. Rats were initially 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 9-week experiment (initial deprived weights in grams [mean ± SEM) 266.2 (±5.4); final deprived weight 298.7 (±7.0)].

Behavioral Procedures

Tests of instrumental responding were performed in operant chambers (28 × 23 × 23 cm; Med Associates). 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 trained on a FR5 schedule for 1 week before being shifted to an alternating food-choice procedure for 3 weeks. On days 1, 3, and 5 of each week the rats were trained to lever press (FR5 schedule) for pellets, and 15–20 g of their standard lab chow (Wayne Rodent Blox, Teklad Premier) was also available on the floor of the operant chamber during the 30-min session; on day 2 and day 4 of each week the animals were trained to lever press (FR5 schedule) for pellets, but lab chow was not available. The total number of lever presses and the amount of lab chow consumed (correcting for spillage) was recorded for each rat.

DA Depletion by Injection of 6-OHDA

Surgery was performed with the rats under pentobarbital anesthesia, and all rats received IP injections of 10.0 mg/kg pargyline 30 min prior to surgery. DA depletions were produced by bilateral injections of 6-OHDA (RBI, Natick, MA) through 30 ga. stainless steel injectors directly into the nucleus accumbens (AP +2.8 mm, ML ±1.4 mm, DV −7.8 mm; incisor bar 5.0 mm above the interaural line). A total of 12.5 μg of the free base of 6-OHDA dissolved in 2.5 μl of 0.1% ascorbic acid (2.5 μl of 5.0 μg/μl 6-OHDA) was injected per side. Control rats received 2.5 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 flow rate of 0.5 μl/min by a Harvard Apparatus syringe pump. One minute was allowed after the injection for diffusion into the tissue.

Neurochemical Analyses for Tissue Dopamine

Following completion of the experiment, rats were decapitated and their brains quickly removed and frozen. A 16 ga. stainless steel tube was used to dissect tissue samples from successive 0.8 mm thick coronal sections cut through the nucleus accumbens, medial striatum, and ventrolateral striatum. Tissue samples from each section were placed in 200 μl of chilled 0.1 N perchloric acid and homogenized. The samples were then centrifuged and the supernatant was analyzed using a high performance liquid chromotography (HPLC) system. The HPLC system 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 (7.0% methanol, 2.8 ml of 0.4 M sodium octyl sulphate, and 0.75 ml of 0.1 M EDTA; pH 4.5) delivered at 0.7 ml/min. An oxidation potential of 0.2 V (working vs. reference electrode) was used. Standards of DA (Sigma Chemical Co.) were assayed before, during, and after the tissue samples.

Experimental Procedure

Rats were trained on the alternating food-choice procedure for 3 weeks (5 days per week, 30-min sessions) prior to surgery. These rats received intracranial injections of either ascorbate vehicle (n = 10) or 6-OHDA (n = 15) into the nucleus accumbens, as described above. Rats were tested on the alternating food-choice procedure, 5 days per week, for 4 weeks (30-min sessions on days 3–7, 10–14, 17–21, and 24–28 postsurgery). To maintain body weight, some rats received supplemental lab chow in their home cage. When all behavioral testing was completed, all rats were sacrificed (28–34 days after surgery), as described above.

Statistical Analysis

Only rats that had DA depletions greater than 75% (i.e., DA levels <25% of the control mean) were analyzed by ANOVA (DA depleted, $n = 8$). The Student's t-test was used to compare DA content between the nucleus accumbens, medial, and ventrolateral striatum. Lever presses were analyzed by calculating responses per day for days 1, 3, and 5 of each week (lab chow present in the operant chamber) and responses per day for days 2 and 4 of each week (chow not available). A factorial ANOVA (DA depletion × food condition) with repeated measures on food condition was performed on these behavioral data, with each week of postsurgical testing being analyzed separately. Analysis of simple main effects was performed to provide further analyses of the ANOVA data (20). Student's t-test was used to compare the average amount of lab chow consumed for the week between the two groups. Percentage of food obtained from lever presses and chow consumption was obtained 3 days per week (on days 1, 3, and 5 of each). Percentage of food obtained by lever pressing was calculated by dividing the amount of food obtained from lever pressing (lever presses divided by 5 multiplied by 0.045 g) by the total amount consumed in the operant chamber (grams of pellets and lab chow). These data were arc-sin transformed and analyzed by Student's t-test. The Pearson product-moment correlation was used to establish relations between neurochemical and behavioral data.

RESULTS

Neurochemical Results

Tissue assay data [Mean (±SEM) ng DA/mg tissue] for control rats ($n = 10$) and DA-depleted rats that were included in the ANOVA analyses (>75% depletions; $n = 8$) were as follows: nucleus accumbens—control 5.12 (±0.63), DA-depleted 1.28 (±0.14); medial neostriatum—control 9.29 (±1.11), DA-depleted 6.45 (±1.08); ventrolateral striatum—control 11.68 (±1.54), DA-depleted 10.52 (±0.86). Only DA levels in the nucleus accumbens were significantly reduced relative to control rats, $t(16) = 5.3, p < 0.05$.

Behavioral Analyses

The total number of lever presses across all 4 weeks of postsurgical testing are shown in Fig. 1. There were no group differences in the 4-day baseline period. There was no overall effect of DA depletion, $F(1, 16) = 3.0$, NS, during week 1; however, there was a significant effect of test day (i.e., presence or absence of lab chow in the operant chamber) on the number of lever presses, $F(1, 16) = 11.1, p < 0.01$. There was also a significant DA depletion × test day interaction, $F(1, 16) = 12.6, p < 0.01$. Analysis of simple main effects indicated that there was a significant suppression of lever pressing in DA-depleted rats relative to controls on the test days when chow was present, $F(1, 16) = 5.0, p < 0.05$, but

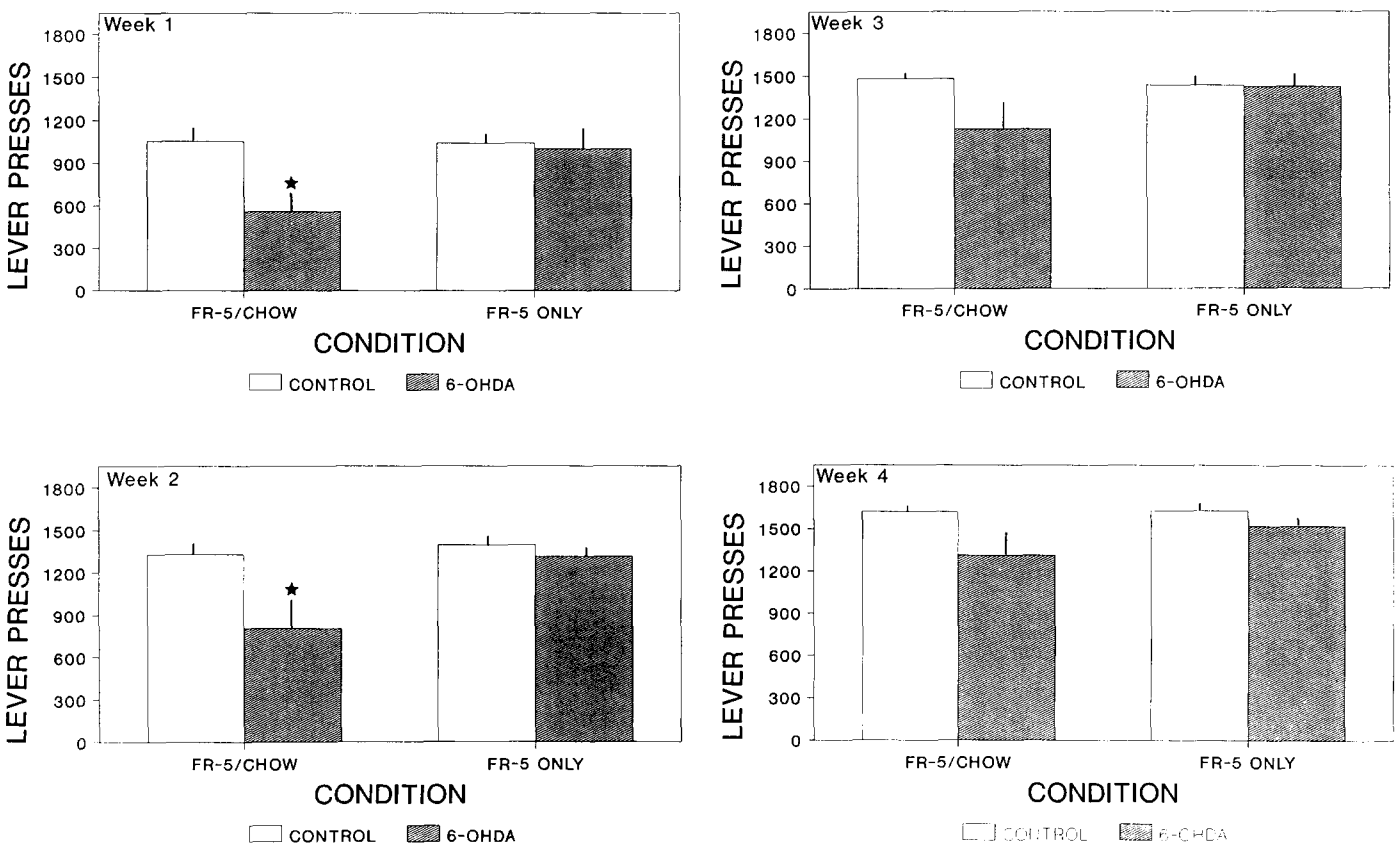

FIG. 1. Mean (±SEM) lever presses for the control and DA-depleted rats during each of the 4 weeks of postsurgical testing. Data are expressed as the lever presses per day for the 3 days when chow was concurrently available (FR-5/CHOW) and the 2 days when chow was not concurrently available (FR-5 ONLY) for each week. (*$p < 0.05$, DA-depleted rats on FR-5/CHOW different from controls on FR-5/CHOW, and also different from DA-depleted rats on FR-5 ONLY).

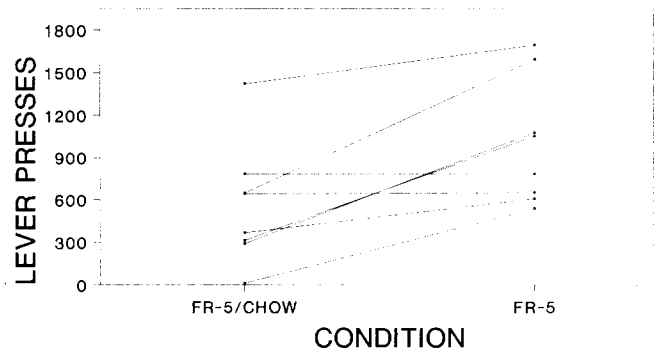

FIG. 2. Lever pressing data for individual DA-depleted rats during the first week of postsurgical testing. Data are expressed as lever presses per day for the 3 days when chow was concurrently available (FR-5/CHOW) and the 2 days when chow was not concurrently available (FR-5). The lines shown connect the data points from each individual rat.

not for the test days when food was not present, $F(1, 16) = 0.03$, NS. Although control rats did not show significant differences in responding between days when chow was present vs. days when chow was not present, $F(1, 16) = 0.02$, NS, DA depletions in the nucleus accumbens resulted in a significant decrease in lever pressing on days when lab chow was concurrently available as compared to days when chow was not available, $F(1, 16) = 21.3, p < 0.01$. There was a significant overall treatment effect on the total number of lever presses during week 2, $F(1, 16) = 4.6, p < 0.05$, as well as a significant effect of test day, $F(1, 16) = 7.9, p < 0.05$. There was also a significant group × test day interaction, $F(1, 16) = 4.6, p < 0.05$. Analysis of simple main effects indicated that there was a significant suppression of lever pressing in DA-depleted rats relative to controls on the test days when chow was present, $F(1, 16) = 6.90, p < 0.05$, but not for the test days when food was not present, $F(1, 16) = 0.17$, NS. Although control rats did not show significant differences in responding between days when chow was present vs. day when chow was not present, $F(1,16) = 0.24$, NS, DA-depleted rats showed a significant decrease in lever pressing on days when lab chow was concurrently available as compared to days when chow was not available, $F(1, 16) = 11.7, p < 0.01$. There were no significant treatment or test-day effects for week 3, $F(1, 16) = 1.8$, NS, $F(1, 16) = 1.2$, NS, respectively. There were no significant treatment or test-day effects for week 4, $F(1, 16) = 3.3$, NS, $F(1, 16) = 2.0$, NS, respectively.

Figure 2 shows lever pressing data for individual rats with DA depletions during the first week of postsurgical testing. In Fig. 2 it can be seen that the presence of chow reduced lever pressing substantially in most DA-depleted rats. It should be emphasized that some of the individual DA-depleted rats showed normal levels of lever pressing when chow was not available (control mean for week 1 = 1040 responses per day when chow was not available) although these same rats showed lower levels of responding when chow was available. Correlational analyses (Pearson's Product-Moment correlation) were performed between accumbens DA levels and lever pressing data during the first week of postsurgical testing on the group of 8 DA-depleted rats. Accumbens DA levels were positively correlated with lever pressing on the days when chow was concurrently available ($r = 0.73, p < 0.05$). There was also a positive correlation between DA levels and lever pressing when chow was not available in the operant chamber, ($r = 0.77, p < 0.05$).

Figure 3 shows the lab chow consumed per day (averaged from days 1, 3 and 5 of each week) for all 4 weeks of postsurgical testing. There were no group differences in the 4-day baseline period. There was a significant increase in consumption of lab chow for rats with DA depletions during week 1, $t(16) = 3.8, p < 0.01$, week 2, $t(16) = 3.2, p < 0.01$, and week 3, $t(16) = 2.6, p < 0.05$, of postsurgical testing. There were no significant differences between groups during week 4 of postsurgical testing, $t(16) = 2.0$, NS. The proportion of food obtained through lever pressing for all 4 weeks of postsurgical testing is shown in Fig. 4. There were no group differences during the 4-day baseline period. Rats with DA depletions obtained a significantly smaller percentage of their food from lever pressing as compared to controls during week 1, $t(16) = 3.6, p < 0.01$, week 2, $t(16) = 3.09, p < 0.05$, and week 3,

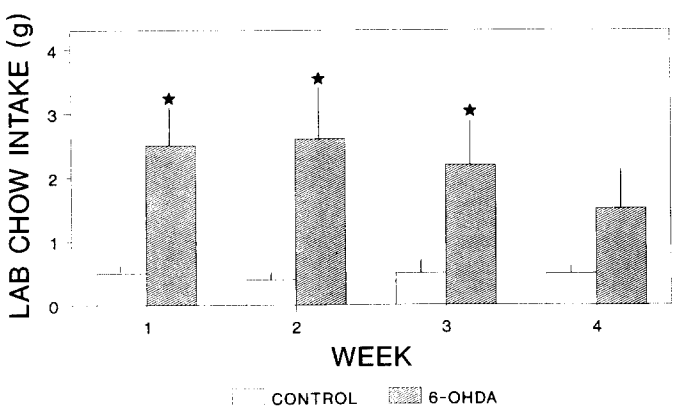

FIG. 3. Mean (+SEM) chow consumption for the control and DA-depleted rats during the 4 weeks of postsurgical testing. Data are expressed as grams consumed per day for the days when chow was available. (*$p < 0.05$, different from control).

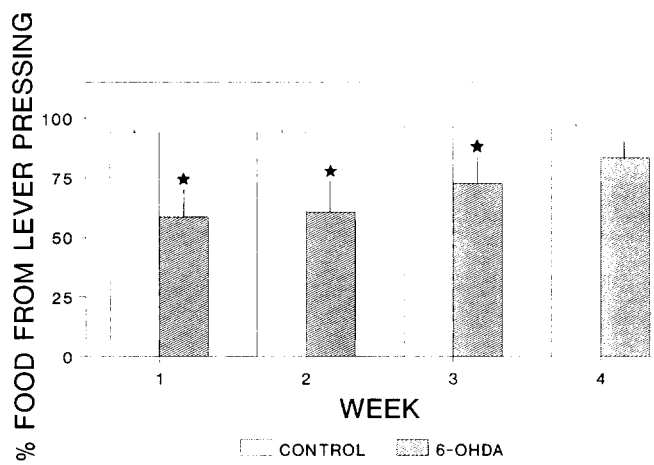

FIG. 4. Mean (±SEM) percent of food obtained from lever pressing for the control and DA-depleted rats during the 4 weeks of postsurgical testing. Data are expressed as the average of the 3 days during which chow was available for each test week. (*$p < 0.05$, different from control).

$t(16) = 2.5$, $p < 0.05$. No significant differences were observed during week 4 of postsurgical testing, $t(16) = 2.0$, NS.

DISCUSSION

Nucleus accumbens DA depletions had only a minor effect on lever pressing rate when chow was not available, and the entire group of DA-depleted rats did not significantly differ from the control group in terms of total number of FR5 responses. There was a significant positive correlation between accumbens DA levels and FR5 lever pressing, which indicates that substantial DA depletions could reduce lever pressing. Nevertheless, even among the four rats that had the lowest levels of accumbens DA, the mean lever pressing rate was approximately 75% of the control mean. These results are consistent with previous studies showing that nucleus accumbens DA depletions produced only a modest suppression of lever pressing rate (26,32,42). With rats responding on a CRF schedule, extensive depletions of accumbens DA had a significant effect on total number of responses only on a single test day [day 3 after surgery; see (26)]. Accumbens DA depletions produced a minor suppression of FR5 lever pressing that was only significant during the first week after DA depletion (42). In both of these previous studies, the average DA levels remaining after 6-OHDA injection were slightly lower than those reported in the present work, which may account for the lack of overall significant effect in the present study. Nevertheless, the results of all these studies indicate that accumbens DA depletions produce only a minor effect on CRF and FR5 lever pressing performance. Such a finding is in marked contrast to the effects of ventrolateral striatal DA depletions, which have been shown to produce substantial and persistent decreases in FR5 responding even among animals with modest depletions (42).

Although accumbens DA depletions had only a minor effect on FR5 response rate when lever pressing was the only source of food available, accumbens DA depletions produced a substantial decrease in FR5 lever pressing when lab chow was concurrently available. In addition, when lab chow was available in the test chamber, the DA-depleted rats showed significant increases in chow consumption. These results replicate previous studies in which the concurrent FR5/feeding procedure was used (7,44). Taken together, these results fail to support the notion that accumbens DA depletions resulted in a general loss of food motivation or a transsituational reduction in the ability of food to act as an appetitive stimulus. Rather, the reductions in lever pressing and concomitant increases in chow consumption that reliably result from accumbens DA depletions indicate that these rats remain directed toward food acquisition and consumption. Similar results have recently been obtained from a T-maze experiment in which different arms of the maze contained high or low densities of food reinforcement. Rats were tested either with or without a barrier that forced them to climb to obtain the higher food density. In that experiment, accumbens DA depletions reduced barrier climbing for the high food density, but had no effect on the selection of the high density of food reinforcement when the barrier was not present (40). Thus, the results of this entire series of experiments do not support the notion that interference with accumbens DA function induces a state of anhedonia or a uniform blunting of all aspects of appetitive motivation.

The present pattern of results indicates that DA in nucleus accumbens is involved in subtle and complex aspects of behavioral function. The increases in chow consumption shown by rats with accumbens DA depletions demonstrate that, in spite of a reduction in lever pressing when chow was available, DA-depleted rats remain directed towards the acquisition and consumption of food. The present results also indicate that the shift from lever pressing to consumption of lab chow following accumbens DA depletions is not due simply to a lever pressing deficit that sets an absolute ceiling on the number of responses that can be emitted. Although nucleus accumbens DA depletions produce substantial effects on FR5 lever pressing rate only when chow is concurrently available, DA depletions in ventrolateral striatum substantially reduce FR5 lever pressing regardless of whether or not chow is offered concurrently (7,42). Ventrolateral striatal DA depletions dramatically reduced feeding rate and impaired forepaw usage during food handling, but accumbens DA depletions were not shown to impair food intake, feeding rate, or forepaw usage (43). Thus, the behavioral effects of accumbens DA depletions do not resemble a general deficit in food motivation, nor do they reflect a pronounced motor disturbance such as that evident in rats with ventrolateral striatal DA depletions (7,16,41,42,43).

The precise behavioral mechanisms that underly the decreases in lever pressing and increases in chow consumption resulting from accumbens DA depletions remain uncertain. Several researchers have suggested that accumbens DA is involved in complex behavioral functions related to motivation, including the performance of "preparatory" behavior (3,4,30), and the modulation of some of the behavioral effects of conditioned stimuli (5,9,18,50,51). Despite a lack of evidence indicating that nucleus accumbens DA depletions produce severe or obvious deficits in fine motor control, it is possible that nucleus accumbens DA depletions produce subtle alterations in aspects of muscle control that do not manifest themselves in terms of a substantial defict in lever pressing. Alternatively, accumbens DA depletions could be producing an impairment in higher-order motor functions that regulate quantitiative features of motor output, such as overall energy expenditure, response speed, or response probability. Evidence indicates that accumbens DA depletions result in a motor slowing that is evident in terms of a modest slowing of the local rate of operant responding (42), a reduction in initial response rate (26,42), and reductions in food-induced locomotor activity (25). Previous work has indicated that decreases in lever pressing and increases in chow consumption in rats with accumbens DA depletions were correlated with decreases in locomotor activity (7). Although it is often implied that there is a strict dichotomy between motor and motivational processes, it has been suggested that accumbens DA is involved in processes that are common to aspects of both motor and motivational function (35,37,38,39). Mogenson and colleagues (28) have suggested that nucleus accumbens is a point of functional interaction between limbic areas involved in motivation and areas of the brain involved in motor control. Thus, nucleus accumbens DA may be involved in behavioral activation, which can be considered as an aspect of motor or sensorimotor function that involves responsiveness to motivational stimuli (25,27,34,36,37,38).

The involvement of nucleus accumbens DA in behavioral activation may be important for the performance of highly active responses that are necessary to obtain access to significant stimuli such as food (29,36,37,38). It has been suggested that accumbens DA is involved in hoarding and foraging behavior (19,36). Studies of foraging in the wild and the laboratory, as well as economic models of instrumental behavior,

suggest that the relations between response costs and benefits such as food reinforcement are important determinants of response allocation (1,6,12,14,15,17,22,23,31,46,47). Experiments using the concurrent FR5/feeding procedure indicate that nucleus accumbens DA depletions do not simply reduce food selection. Instead, accumbens DA depletions appear to set constraints upon which response is selected to gain access to food. Although the precise characteristics of these constraints are uncertain, the net effect of accumbens DA depletion is to alter the relative allocation of responses with different kinetic requirements (38).

ACKNOWLEDGEMENT

This research was supported by a grant from the National Science Foundation (BNS 9009613).

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