Pharmacology Biochemistry and Behavior, Vol. 59, No. 3, pp. 557–566, 1998

0091-3057/98 $19.00 + .00

ELSEVIER

PII S0091-3057(97)00544-3

The Role of Accumbens Dopamine in Lever Pressing and Response Allocation: Effects of 6-OHDA Injected into Core and Dorsomedial Shell

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Received 17 January 1997; Revised 19 May 1997; Accepted 19 June 1997

SOKOLOWSKI, J. D. AND J. D. SALAMONE. *The role of accumbens dopamine in relative response allocation: Effects of 6-OHDA injected into core and dorsomedial shell.* PHARMACOL BIOCHEM BEHAV **59**(3) 557–566, 1998.—Three experiments investigated the behavioral effects of injections of the neurotoxic agent 6-hydroxydopamine (6-OHDA) into the core or shell of the nucleus accumbens. In the first experiment, it was observed that injections of 6-OHDA into either core or shell had no significant effect on variable interval 30-s responding. In Experiment 2, responding on a fixed ratio 5 (FR5) schedule was impaired by 6-OHDA injections in the core, but not the shell. Rats with core injections of 6-OHDA showed significant alterations in the relative distribution of interresponse times, which were indicative of reductions in the maximal rate of responding and increases in the number of pauses. In the third experiment, rats were tested using a lever-pressing/chow-feeding procedure, in which a preferred food (Bioserve pellets) was available by pressing a lever on a FR5 schedule, but a less preferred food (lab chow) was also available concurrently in the test chamber. Untreated rats usually pressed the lever at high rates to obtain the food pellets and ate little of the lab chow. After training, dopamine depletions were produced by injections of 6-OHDA directly into the core or dorsomedial shell subregions. Injections of 6-OHDA into the core significantly decreased lever pressing for food pellets, increased lab chow consumption, and decreased the relative amount of food obtained by lever pressing. Dorsomedial shell injections of 6-OHDA had no significant effects on either lever pressing or lab chow consumption. Neurochemical results indicate that injections of 6-OHDA in the shell produced substantial depletions in the shell that were somewhat selective; however, injections of 6-OHDA into the core tended to deplete both core and shell. Correlational analyses revealed that decreases in FR5 lever pressing were associated with dopamine levels in the core, but not the shell. The present results indicate that substantial depletions of dopamine in the dorsomedial shell are not sufficient for suppressing reinforced lever pressing, and indicate that dopamine depletions must include the core area to impair performance on these tasks. The lack of effect of accumbens dopamine depletions on VI30 responding are consistent with the notion that accumbens dopamine depletions affect responding on schedules that generate a high rate of responding (FR5), but not those that generate a moderate rate of responding (e.g., VI30 s). The results of the concurrent FR5/chow-feeding experiment indicate that rats with accumbens dopamine depletions remain directed towards the acquisition and consumption of food. These results suggest that dopamine in the core region of accumbens sets constraints upon the selection of food-related behaviors, and that core dopamine depletions alter the relative allocation of food-related responses. © 1998 Elsevier Science Inc.

Dopamine Reinforcement Operant Motivation Movement Behavioral economics

SEVERAL studies have shown that antagonism of brain dopamine (DA) receptors impairs instrumental lever pressing (15,47–52,69–72). Depletions of DA in the ventrolateral neostriatum lead to severe motor impairments that are associated with deficits in lever pressing (10,11,55). In addition, depletions of DA in the nucleus accumbens have been shown to reduce lever pressing on some schedules [e.g., fixed ratio 5; (55)], while responding on other schedules is relatively unaf-

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fected (37,45,56). Various hypotheses have been offered to characterize the role of DA in instrumental behavior, and it has been suggested that interference with DA impairs "reinforcement" or "motivational" processes, as well as "motor" function (44,48–52,68,70). Considerable evidence indicates that the suppression of lever pressing induced by DA antagonists does not depend upon a general impairment of food motivation. Several reports have demonstrated that low/moderate doses of DA antagonists that decrease lever pressing for food or water leave food and water consumption unaffected (16,31–34,46). Within the last few years, a choice procedure was developed that has allowed for an assessment of the effects of DA antagonists or DA depletions on lever pressing and lab chow intake (58). In this concurrent lever pressing/feeding task, a preferred food (Bioserve pellets) is available by pressing a lever on a fixed ratio (FR) schedule, but a less preferred food (lab chow) is also available concurrently in the test chamber. Usually, untreated rats on FR1 or FR5 schedules obtain most of their food by lever pressing for the preferred food, and eat little of the available lab chow. Increasing ratio value up to FR10 or FR20 to increase response costs led to a relative decrease in food obtained through lever pressing and an increase in chow intake (52). Systemic or intra-accumbens injections of haloperidol were shown to reduce FR5 lever pressing but significantly increase chow consumption (58). Using this lever pressing/feeding task, decreases in lever pressing and increases in chow consumption have been observed after acute treatment with the nonselective DA antagonist flupenthixol, the D_2 antagonist haloperidol, and the D_1 antagonist SCH 23390 (13,58), as well as repeated daily injections of haloperidol (54). Haloperidol injections produced effects different than those observed with prefeeding, which acted to decrease both lever pressing and chow consumption (54). In addition, systemic haloperidol did not alter the preference for pellets over lab chow in free-feeding preference tests (58). These results were interpreted to mean that low doses of DA antagonists, or accumbens DA antagonism, decreased lever pressing but did not alter the unconditionally rewarding characteristics of food consumption (13,58). Instead, it was suggested that DA is involved in the process of setting constraints upon which food-related behavior is selected in a particular situation, and that dopamine antagonism alters the relative allocation of food-related responses.

Several studies have been conducted to investigate which DA terminal regions are involved in the relative allocation of food-related responses. Decreases in lever pressing and increases in chow intake have been shown to result from local injections of haloperidol into nucleus accumbens (58). Depletions of DA produced by injections of 6-hydroxydopamine (6-OHDA) directly into the accumbens also were shown to decrease lever pressing and increase chow intake (9,12,58). In contrast, ventrolateral neostriatal DA depletions have been shown to produce profound motor impairments that decrease both lever pressing and chow consumption (10–12,23,55,57). Thus, nucleus accumbens DA depletions produce effects that are quite distinct from those produced by prefeeding to reduce food motivation, and also are very different from the severe motor impairments produced by ventrolateral neostriatal DA depletions. Nucleus accumbens DA depletions also have been shown to alter response allocation in a T-maze cost/benefit task (8,53).

Previous studies of the effects of accumbens DA depletions on lever pressing [e.g., (55)] and the concurrent lever pressing/feeding task [e.g., (9,58)] have involved injections of 6-OHDA into a single injection site adjacent to the anterior commissure (1.4 mm from midline). Recent anatomical evidence indicates that the nucleus accumbens is divided into distinct subregions; there is a "core" region that surrounds the anterior commissure, and a "shell" region that is medial and ventral to the core (3,4,18,38,63,73–75). Several studies have focussed upon the involvement of core and shell subregions of accumbens in various behavioral functions, including stress (14,20,25), locomotor activity (19,42), latent inhibition (68), oral motor activity (41), drug self-administration (7), sensorimotor gating (67), and feeding (35,36). It has been suggested that nucleus accumbens shell is important in mediating the rewarding effects of stimuli (24). However, no behavioral studies to date have utilized injections of 6-OHDA to deplete DA in these two regions so that effects on lever pressing tasks for food reinforcement could be assessed. Thus, the present study was conducted to compare the effects of 6-OHDA injected into the core (1.8 mm from midline) and the dorsomedial region of shell (1.1 mm from midline). The medial/lateral coordinates used in the present study were the same as those used by Maldonado-Irizarry et al. (35,36). The parameters for 6-OHDA injection (i.e., volume, concentration) were the same as those used in several previous studies (9,12,55), so that the present results could be compared with these previous findings.

Three behavioral tasks were used to assess the effects of core and shell injections of 6-OHDA on food reinforced responding. In the first experiment, rats were trained to respond on a variable-interval 30-s (VI30) schedule. This schedule was used because it generates a moderate rate of responding. For the second experiment, a FR5 schedule was used. Previous work has shown that the FR5 schedule, which generates a high rate of responding, is sensitive to the effects of accumbens DA depletions (55). As well as describing behavioral output in terms of global measures such as total number of responses, it is also important to include more detailed behavioral measures than total lever presses (10,11,15,55,56). For that reason, the response pattern as expressed by interresponse times (IRTs) was also analyzed. IRTs are measured by computing the time in between each lever press, which is the reciprocal of the local rate of responding; the pattern of responding is then determined by sorting each IRT into a time bin. IRT distributions have been used in several experiments to analyze temporal patterns of responding [e.g. (55,56,60)]. For the third experiment, the concurrent FR5/chow feeding procedure was used to study the effects of core and shell injections of 6-OHDA.

METHOD

Subjects

A total of 90 male Sprague–Dawley rats (Harlan Sprague–Dawley, Indianapolis, IN) were used in these experiments. Rats were housed in a colony maintained at 23°C with a 12 L: 12 D cycle (lights on at 0700 h). 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 experiment. Water was available ad lib in the home cages.

Behavioral Procedures

Tests of lever pressing and chow consumption were conducted 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 one of three behavioral procedures. In the first experiment, rats were trained to lever press on the VI30 schedule. With this schedule, rats receive reinforcement following the first lever press after an interval of time that averages 30 s over each test session. During testing on the VI30 schedule, the total number of lever presses was recorded, and several other measures related to the IRT also were obtained. A second group of animals was trained on the FR5 schedule alone (i.e., without freely available lab chow) for 3 weeks before surgery. The total number of lever presses and interresponse times (IRTs) were recorded for each rat, and IRT distributions were calculated. IRT distributions provide a measure of the pattern of responding by sorting each lever press into a "time bin" based on the length of the IRT [see also (55)]. IRTs in the present study were sorted into 11 time bins; 10 bins that were 250 ms in length (i.e., 0–250 ms, 250–500 ms, etc., up to 2.25–2.5 s) and bin 11, which included all IRTs greater than 2.5 s. For the third experiment, rats were trained to lever press on the FR5 schedule for 2 weeks before being shifted to the concurrent FR5/chow procedure for 2 weeks. In this procedure, the rats could press the lever on a FR5 schedule for pellets, while 15–20 g of their standard lab chow (Agway Rodent Diet) was also available on the floor of the operant chamber during the 30 min session. 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 (50 mg/kg) and all rats received IP injections of 20.0 mg/kg pargyline 30 min prior to surgery. DA depletions were produced by bilateral injections of 6-OHDA (Research Biochemicals Inc., Natick, MA) through 30 gauge stainless steel injectors directly into the nucleus accumbens (CORE: AP +2.8 mm, ML ±1.8 mm, DV −7.8 mm; SHELL: AP +2.8 mm, ML ±1.1 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. Rats in the control groups received 2.5 μl per side of the 0.1% ascorbate solution at the same sites as the 6-OHDA–treated rats (VI30: four at the core site, five at the shell site; FR5: five at the core site, four at the shell site; FR5/chow feeding: four at the core site, five at the shell site). The injection was driven at a flow rate of 0.5 μl/min by a Harvard Apparatus syringe pump.

Neurochemical Analyses for Tissue Dopamine

Following completion of each experiment, rats were decapitated and their brains quickly removed and frozen. An 18 gauge stainless steel tube, which was bent slightly into an oval shape, was used to dissect tissue samples from a coronal section (0.75 mm thick) cut through the nucleus accumbens core and shell. In addition, a 16 gauge stainless steel tube was used to dissect tissue samples from a coronal section through the ventrolateral neostriatum. Tissue samples from each brain section were placed in 200 μl of chilled 0.1 N perchloric acid and homogenized. The samples were centrifuged, and the supernatant was then analyzed using a high-performance liquid chromatography system that has been described previously (9–12,55). Standards of DA (Sigma Chemical Co.) were assayed before, during, and after the samples.

Experimental Procedure

In the first two operant experiments, different groups of rats were trained on either the VI30 or FR5 operant schedule for three weeks (5 days per week, 30-min sessions) prior to surgery. These rats received intracranial injections of either ascorbate vehicle (VI30 $n = 9$; FR5 $n = 9$) or 6-OHDA into the core (VI30 $n = 10$; FR5 $n = 11$) or shell (VI30 $n = 10$; FR5 $n = 11$) regions of the nucleus accumbens as described above. Rats were then tested 5 days per week for 3 weeks (30-min sessions on days 3–7, 10–14, and 17–21 postsurgery). In the concurrent FR5/chow feeding study (Experiment 3), rats were trained as described above for 2 weeks (5 days per week, 30-min sessions) prior to surgery. These rats received intracranial injections of either ascorbate vehicle ($n = 9$) or 6-OHDA into the core ($n = 10$) or shell ($n = 11$) regions of the nucleus accumbens as described above. After surgery, rats were tested 5 days per week for 3 weeks (30-min sessions on days 3–7, 10–14, and 17–21 postsurgery). For all three experiments, some rats received additional lab chow in their home cage to maintain body weight. Upon completion of the behavioral testing, rats were sacrificed (28–31 days after surgery) as described above.

Statistical Analyses

Only rats that had DA depletions greater than 80% (i.e., DA levels <20% of the control mean) were analyzed by ANOVA. Based upon this criterion, a few rats (VI30: one core, one shell; FR5: three core, three shell;. FR5/chow: two core, and two shell) were not included in the ANOVAs, although these rats were included in the correlational analyses. The ANOVA design was a 3 (week) × 3 (group) factorial ANOVA with repeated measures on the week factor. In the VI30 experiment, lever presses were analyzed using repeated measures ANOVA on weekly averages of all measures. For rats in the FR5 experiment, two major behavioral parameters were analyzed. Lever presses were analyzed using 3 × 3 factorial ANOVA after calculating the average number of responses per week for each week of postsurgical testing. Weekly averages of each IRT bin (expressed as percent of total responses) were analyzed using a 3 group × 11 bin factorial ANOVA, with repeated measures on the bin factor; these data were analyzed as percent of total responses to correct for group differences in responding so that the relative distribution of IRTs could be determined. A separate analysis was performed for each week of postsurgical testing. A significant group × bin interaction was interpreted as an alteration in the pattern of the relative IRT distribution across groups. Analysis of simple effects (27) was used to identify the source of the interaction by signifying which IRT bins showed significant differences. For those IRT bins in which a significant difference was found, paired comparisons between groups were made with the Tukey test. In the concurrent FR5/chow feeding experiment, three major behavioral parameters were analyzed. Lever presses were analyzed by calculating a weekly average for each of the 3 weeks of postsurgical testing. Chow intake was analyzed by calculating the weekly average of chow intake (in grams) for each of the 3 weeks of testing. Percentage of food obtained by lever pressing was calculated by dividing the amount of food obtained from lever pressing (lever presses divided by five multiplied by 0.045 g) by the total amount consumed in the operant chamber (grams of pellets and lab chow), and obtaining a weekly average. Each of these measures was analyzed by a 3 × 3 factorial ANOVA with repeated measures on the week factor. For Experiments 2 and

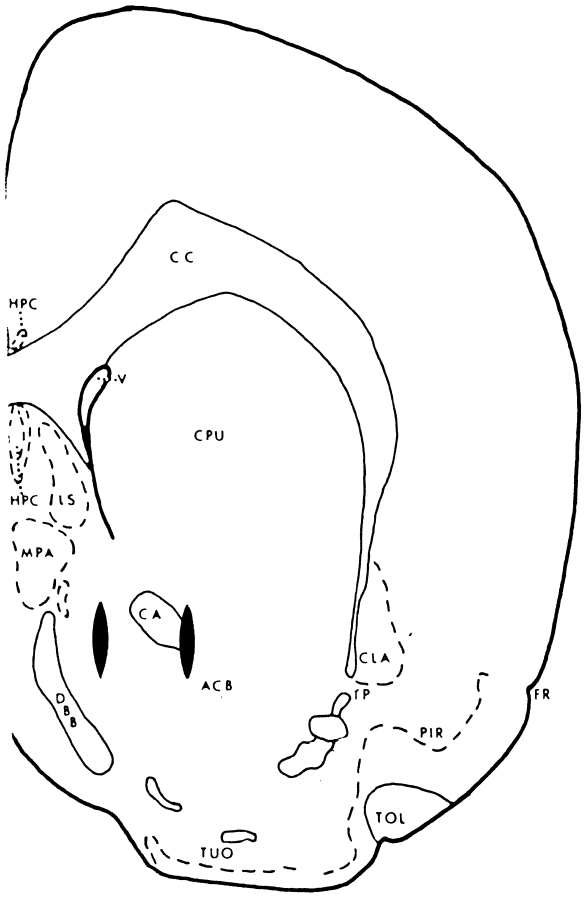

FIG. 1. Representative placement sites in shell (medial) and core (lateral) of the nucleus accumbens (ACB). Injections were bilateral, although only one side is shown. Figure is modified from (40).

3, planned comparisons involving the overall error term (26) were used to identify group differences. The Pearson product–moment correlation was used to study the relation between various neurochemical and behavioral measures.

RESULTS

Neurochemical Results

As shown in Tables 1–3, rats receiving injections of 6-OHDA in either the nucleus accumbens core or shell (see Fig. 1) had significant depletions of DA in both regions, as demonstrated by ANOVA. For the analysis of nucleus accumbens core DA, ANOVA revealed an overall significant effect of the 6-OHDA treatment in all three experiments [Table 1, $F(2, 24) = 88.67$, $p < 0.001$; Table 2, $F(2, 21) = 26.91$, $p < 0.001$.; Table 3, $F(2, 22) = 23.99$, $p < 0.001$]. For all three experiments, planned comparisons showed that both the core and shell 6-OHDA groups had significant depletions of core DA. Post hoc comparisons with the Tukey test indicated that the core and shell groups significantly differed from each other in all three experiments, with the rats receiving core injections of 6-OHDA having significantly lower levels of core DA than rats with shell injections. ANOVA also revealed an overall significant effect of 6-OHDA injection into the nucleus accumbens shell [Table 1, $F(2, 24) = 172.90$, $p < 0.001$; Table 2, $F(2, 21) = 106.84$, $p < 0.001$; Table 3, $F(2, 22) = 75.16$, $p < 0.001$]. Planned comparisons demonstrated that both the core and shell 6-OHDA groups had significant DA depletions compared to the vehicle group. Rats in the core and shell 6-OHDA groups did not differ in terms of shell DA levels. Analysis of DA levels in the ventrolateral neostriatum did not show any significant effects of 6-OHDA treatment for any of the experiments.

TABLE 1

MEAN (±SEM) TISSUE LEVELS OF DA (ng DA/mg TISSUE) IN CORE AND SHELL NUCLEUS ACCUMBENS AND VENTROLATERAL STRIATUM (VLS) FOR RATS IN THE VI30 EXPERIMENT

	Region		
Group	VLS	Core	Shell
VEH ($n = 9$)	14.99	3.96	4.38
	(1.17)	(0.14)	(0.30)
Core ($n = 9$)	12.20	0.36*	0.30*
	(0.91)	(0.04)	(0.07)
		91.0%	93.2%
Shell ($n = 9$)	14.33	2.06*†	0.36*
	(0.54)	(0.30)	(0.04)
		48.0%	91.8%

The percentage depletion of each nucleus accumbens subregion in the core and shell groups is also expressed.
*$p < 0.05$, different from vehicle control.
†$p < 0.05$, different from core group.

Behavioral Analyses (VI30)

As shown in Fig. 2, no significant differences in VI30 lever pressing were found between groups using repeated measures ANOVA, $F(2, 24) = 0.16$, NS. There was a significant effect of week, $F(2, 48) = 7.61$, $p < 0.01$, which indicates that all groups of animals exhibited an increase in responding over the 3 weeks of testing. There was no significant interaction between week and group, $F(4, 48) = 0.65$, NS. Several other detailed parameters of responding related to the IRT were ex-

TABLE 2

MEAN (±SEM) TISSUE LEVELS OF DA (ng DA/mg TISSUE) IN CORE AND SHELL NUCLEUS ACCUMBENS AND VENTROLATERAL STRIATUM (VLS) FOR RATS IN THE FR5 EXPERIMENT

	Region		
Group	VLS	Core	Shell
VEH ($n = 8$)	15.76	5.05	5.10
	(0.83)	(0.49)	(0.41)
Core ($n = 8$)	12.96	0.51*	0.47*
	(0.53)	(0.06)	(0.15)
		89.9%	90.7%
Shell ($n = 8$)	13.11	2.21*†	0.52*
	(1.33)	(0.58)	(0.09)
		56.1%	89.8%

The percentage depletion of each nucleus accumbens subregion in the core and shell groups is also expressed.
*$p < 0.05$, different from vehicle control.
†$p < 0.05$, different from core group.

TABLE 3

MEAN (±SEM) TISSUE LEVELS OF DA (ng DA/mg TISSUE) IN CORE AND SHELL NUCLEUS ACCUMBENS AND VENTROLATERAL STRIATUM (VLS) FOR RATS IN THE FR5/FOOD CHOICE EXPERIMENT

	Region		
Group	VLS	Core	Shell
VEH (n = 8)	9.68	3.83	3.98
	(0.94)	(0.37)	(0.24)
Core (n = 8)	8.46	0.26*	0.37*
	(0.84)	(0.04)	(0.07)
		93.2%	90.7%
Shell (n = 9)	8.68	2.35*†	0.41*
	(0.89)	(0.35)	(0.03)
		38.7%	89.6%

The percentage depletion of each nucleus accumbens subregion in the core and shell groups is also expressed.

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

†$p < 0.05$, different from core group.

amined (data not shown); there were no significant effects of 6-OHDA on any of these parameters.

Behavioral Analyses (FR5)

In the FR5 experiment, repeated-measures ANOVA revealed a significant overall effect of DA depletion on lever pressing, $F(2, 21) = 20.90$, $p < 0.01$. Planned comparisons showed a significant decrease in lever pressing relative to the control group for all 3 postsurgical weeks in the core group, $F(1, 21) = 24.0$, $p < 0.01$, but no significant decrease in the shell group, $F(1, 21) = 1.4$, NS, as shown in Fig. 3 . There was a significant effect of week, $F(2, 42) = 99.27$, $p < 0.001$, demonstrating that all three group's performance improved over the testing period, but there was no significant interaction. The results of the analyses of IRT bins are shown in Fig. 4A–C. For all 3 weeks of postsurgical testing, there were significant group × bin interactions [week 1, $F(20, 210) = 6.1$, $p < 0.001$; week 2, $F(20, 210) = 3.9$, $p < 0.001$; week 3, $F(20, 210) = 2.2$, $p < 0.01$]. The general effect of injections of 6-OHDA into the core was to reduce the relative number of IRTs in the fastest IRT bin (0–250 ms), and to increase the relative number of IRTs in the last time bin (>2.5 s; see Fig. 4A–C). Pearson's correlation between DA levels and lever pressing on the FR5 operant schedule indicated that, across all three groups of animals (df = 29), there was a significant correlation between core DA levels and number of lever presses in the first week post surgery ($r = 0.67$, $p < 0.01$). Total accumbens DA (core + shell) showed a modest but significant correlation with number of responses in the first week ($r = 0.53$, $p < 0.05$), while shell DA was not significantly correlated with number of responses in the first week ($r = 0.33$, NS). Core DA levels also were significantly correlated with the percentage of responses in the fastest bin category in week 1 (i.e., 0–250 ms; $r = 0.44$, $p < 0.05$), and inversely correlated with the percentage of IRTs in the slowest bin category in week 1 (i.e., >2.5 s, $r = -0.73$, $p < 0.01$).

Behavioral Analyses (FR5/Chow Feeding)

Repeated measures ANOVA revealed several significant effects of DA depletion in those animals injected with 6-OHDA in the nucleus accumbens core. Although some rats that received injections of 6-OHDA into accumbens shell tended to show changes in responding that were similar to those shown by rats with core injections, there were no significant effects of shell 6-OHDA injections. In the analysis of lever pressing (Fig. 5), the overall ANOVA indicated a significant effect of 6-OHDA treatment, $F(2, 22) = 3.72$, $p < 0.05$. Planned comparisons demonstrated that rats that received core injections of 6-OHDA showed a significant decrease in the number of lever presses for the 3-week testing period compared to the

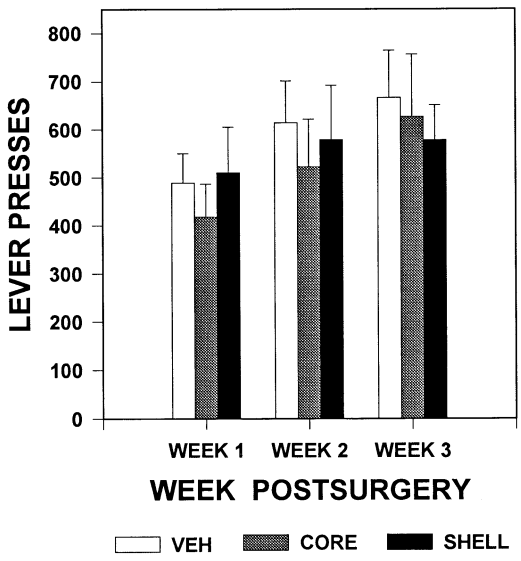

FIG. 2. Mean (+SEM) number of lever presses per day during the 3 weeks of postsurgical testing on the VI30 operant schedule. Means shown are for vehicle, 6-OHDA (core), and 6-OHDA (shell) treatment groups.

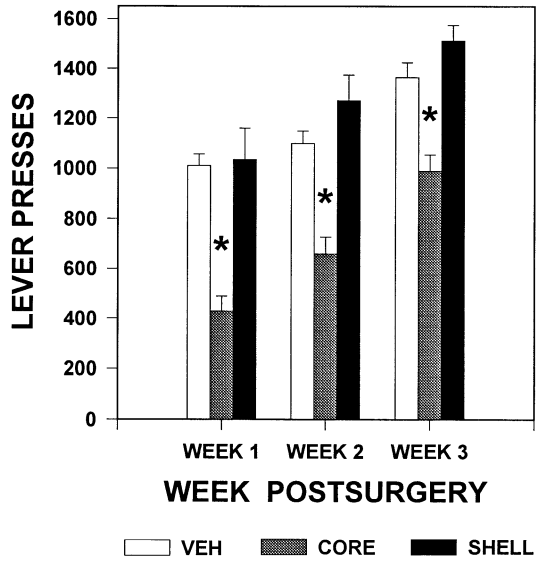

FIG. 3. Mean (+SEM) number of lever presses per day for each of the 3 weeks of postsurgical testing on the FR5 operant schedule for rats in the vehicle, 6-OHDA (core), and 6-OHDA (shell) groups. *$p < 0.05$, core significantly lower than control.

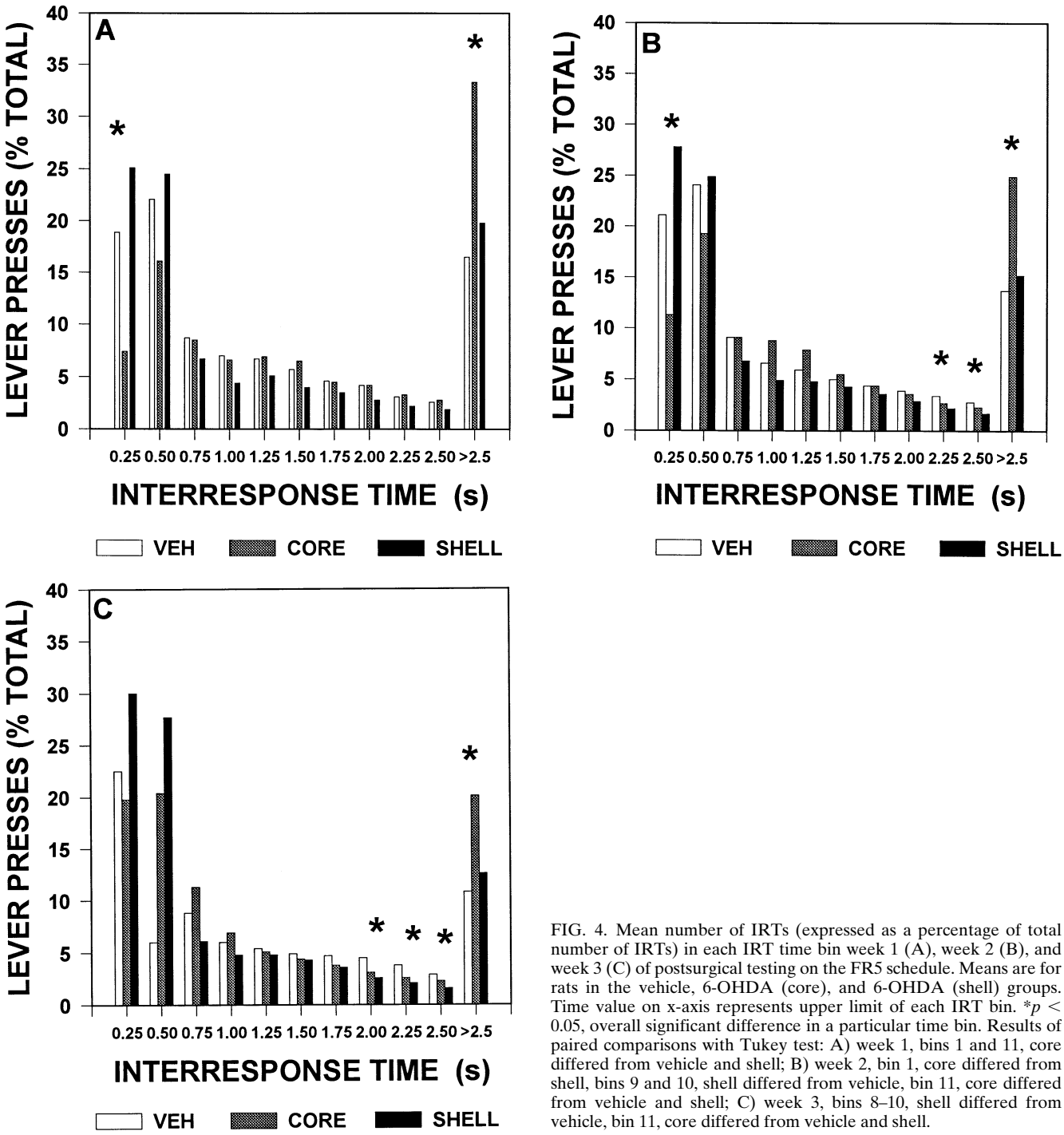

FIG. 4. Mean number of IRTs (expressed as a percentage of total number of IRTs) in each IRT time bin week 1 (A), week 2 (B), and week 3 (C) of postsurgical testing on the FR5 schedule. Means are for rats in the vehicle, 6-OHDA (core), and 6-OHDA (shell) groups. Time value on x-axis represents upper limit of each IRT bin. *$p <$ 0.05, overall significant difference in a particular time bin. Results of paired comparisons with Tukey test: A) week 1, bins 1 and 11, core differed from vehicle and shell; B) week 2, bin 1, core differed from shell, bins 9 and 10, shell differed from vehicle, bin 11, core differed from vehicle and shell; C) week 3, bins 8–10, shell differed from vehicle, bin 11, core differed from vehicle and shell.

control group, $F(1, 22) = 7.43$, $p < 0.05$, while rats in the shell group did not significantly differ from controls, $F(1, 22) = 2.03$, NS. There was also a significant effect of week, $F(2, 44) = 34.44$, $p < 0.001$, but no interaction between treatment group and week, $F(4, 44) = 1.26$, NS. In the analysis of chow consumption (Fig. 6), ANOVA revealed an overall effect of 6-OHDA treatment on the amount of lab chow consumed, $F(2, 22) = 4.46$, $p < 0.05$. Rats in the core group were found to eat a significantly larger amount of lab chow than control animals, as revealed by planned comparisons, during the entire postsurgical period, $F(1, 22) = 8.70$, $p < 0.05$, but rats in the shell group only tended to show a small, nonsignificant increase in lab chow consumption, $F(1, 22) = 3.67$, NS. There was no significant effect of week, $F(2, 44) = 0.34$, NS, and no significant week $\times$ group interaction, $F(4, 44) = 0.39$, NS. Finally, ANOVA indicated a significant overall effect of 6-OHDA treatment on the relative amount of food obtained from lever pressing, $F(2, 22) = 4.28$, $p < 0.05$. Planned comparisons showed that

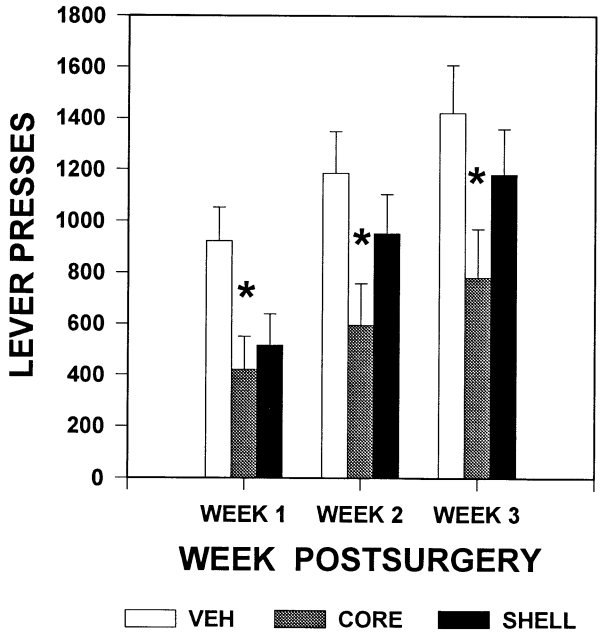

FIG. 5. Mean (+SEM) number of lever presses for each week of postsurgical testing on the FR5/chow-feeding choice procedure. Means shown are for vehicle-treated, 6-OHDA–treated (core), and 6-OHDA–treated (shell) groups. *$p < 0.05$, core significantly lower than vehicle.

rats receiving the core injections obtained a significantly smaller percentage of their food from lever pressing for all 3 weeks of postsurgical testing, as shown in Fig. 7, $F(1, 22) = 8.52$, $p < 0.05$, but rats in the shell group did not significantly differ from control rats, $F(1, 22) = 2.79$, NS. ANOVA found no significant effect of week, $F(2, 44) = 1.66$, NS, and no significant week × group interaction, $F(4, 44) = 0.30$, NS. Pearson's correlation was used to analyze the relationship between all three behavioral measures during the first week postsurgery and DA levels in either the nucleus accumbens core or shell or both regions together. Across all three groups of rats, the three behavioral measures were significantly correlated ($p < 0.05$) with core DA, shell DA, and total accumbens DA [$df = 28$, core DA: lever pressing ($r = 0.41$), chow intake ($r = -0.46$), percent food from lever pressing ($r = 0.45$); shell DA: lever pressing ($r = 0.5$), chow intake ($r = -0.49$), percent food from lever pressing ($r = 0.49$); total accumbens DA (core + shell): lever pressing ($r = 0.49$), chow intake ($r = -0.51$), percent food from lever pressing ($r = 0.51$)].

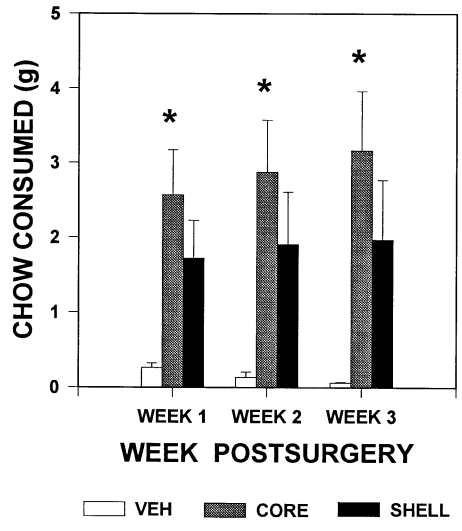

FIG. 6. Mean (+SEM) amount of lab chow consumed (in grams) for each of the 3 weeks of postsurgical testing. Data shown are for the vehicle-treated control group and 6-OHDA–treated (core) and 6-OHDA–treated (shell) groups. *$p < 0.05$, core significantly greater than vehicle.

DISCUSSION

In these experiments it was observed that the behavioral effects of injections of 6-OHDA into the nucleus accumbens can vary greatly, depending upon the site of injection and the behavioral task employed. There were no significant effects of core or shell 6-OHDA injections on VI30 responding. Following core injections of 6-OHDA, lever pressing on the FR5 schedule was significantly decreased, and the distribution of IRTs was substantially altered. On the concurrent FR5/chow feeding task, core injections of 6-OHDA substantially decreased lever pressing but increased chow consumption. Injections of 6-OHDA into the shell region had no significant effects on total number of responses for any of the lever-pressing tasks being studied. Thus, the effects previously reported for intra-accumbens injections of 6-OHDA in several studies [e.g., (9,12,55,58) were produced by similar injections of 6-OHDA into the core, but not the dorsomedial shell.

In the VI30 experiment, injections of 6-OHDA into either the core or the shell had no significant effects on operant re-

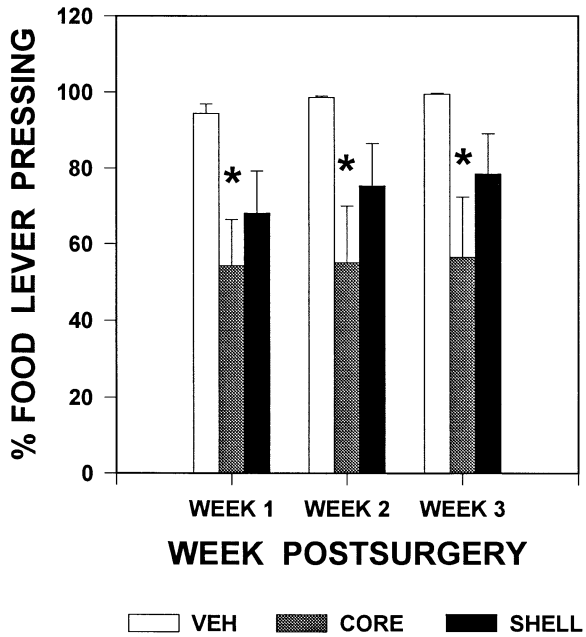

FIG. 7. Mean (+SEM) percentage of food obtained from lever pressing for each week of postsurgical testing. Means shown are for control, 6-OHDA–treated (core), and 6-OHDA–treated (shell), groups. *$p < 0.05$, core significantly less than vehicle.

sponding. Previous research has indicated that the effects of 6-OHDA injected into nucleus accumbens can vary widely, depending upon the lever-pressing schedule being used. Responding on a continuous schedule, which generates low response rates (37,56), was only marginally impaired by DA-depleting lesions in the nucleus accumbens. Roberts et al. (45) reported that accumbens DA depletions, which severely impaired cocaine self-administration, had only mild and transient effects upon variable ratio 2.5 responding for food (which generated about 250 responses per 15 min). Yet, accumbens DA depletions have been shown to impair FR5 responding [Experiment 2 above, see also (55)], and this schedule typically is characterized by high baseline rates or responding. Taking all of these data into account, it appears as though accumbens DA depletions have greater effects on schedules that generate high rates of responding, and little or no effect on schedules characterized by low rates of responding.

In the FR5 experiment, deficits in lever pressing were observed to occur only in the group that received 6-OHDA injections in the core. Rats in the core 6-OHDA group displayed a significant decrease in lever pressing for the 3 weeks of postsurgical testing compared to the control group, while the shell 6-OHDA rats were virtually indistinguishable from the vehicle-treated animals. Similarly, rats in the core group were found to have an altered response pattern compared to the vehicle group. The reduction in overall response rate was characterized by significant alterations in the relative distribution of IRTs. Rats treated with 6-OHDA in the core of the nucleus accumbens had a significantly smaller percentage of responses in the first (i.e., fastest, 0–0.250 s) IRT bin during the first 2 weeks of testing, and a significantly larger percentage in the last (i.e., slowest, >2.5 s) IRT bin for all 3 weeks of testing. The effects of core 6-OHDA injections on the distribution of IRTs in the present study were similar to the effects previously seen following 6-OHDA infusions into a more medial nucleus accumbens core site [1.4 mm lateral; (55)]. In an investigation of CRF responding (56), it also was shown that accumbens DA depletions reduced the relative number of fast IRTs; this pattern was different from extinction, which decreased responding but led to a bursting pattern that manifested itself as an increase in the relative number of fast IRTs (56). Together with other studies (55,56), the present results are consistent with the notion that depletions of core DA lead to an increase in the number of pauses in responding, and also produce a motor slowing that is characterized by a reduction in the relative number of fast interresponse times.

Although injections of 6-OHDA into the core reduced responding on the FR5 schedule, it is unlikely that this effect occurred because of a general disruption of food motivation. In the concurrent FR5/chow feeding test, injections of 6-OHDA into the core, but not the shell, of the nucleus accumbens produced large, long-lasting decreases in lever pressing that were accompanied by increases in chow consumption. The results from the core 6-OHDA injection group in the present study were very similar to those effects seen in several previous reports in which 6-OHDA was injected into a more medial core site [i.e., 1.4 mm lateral; (9,12,58)]. In a related series of experiments, nucleus accumbens DA depletions affected response allocation in a T-maze in which a rat must climb a barrier to obtain a high density of food reinforcement. After nucleus accumbens DA depletions, rats chose not to climb the barrier, but instead consumed a lower density of food reinforcement in an adjacent arm with no barrier (8,53). Thus, considerable evidence indicates that interference with accumbens DA does not produce a general loss of food motivation (2,6,8,9,12,28, 53,58), as DA-depleted rats remain directed toward the acquisition and consumption of food. Because several behavioral investigators have emphasized that primary motivation is a fundamental aspect of reinforcement (5,50,52,64–66), the present results further underscore that important aspects of the reinforcement process remain intact after accumbens DA depletions. Accumbens DA depletions do not appear to blunt the unconditioned reinforcing properties of food, but instead these depletions alter the relative allocation of instrumental responses with different requirements (8,9,12,58). Several behavioral studies have demonstrated that operant responding is an adaptation to constraint, and that economic variables such as response "costs" affect behavioral output (1,17,21,22,26,29,30, 39,43,61,62). Although it is not certain which precise factors underlie the shift in response allocation produced by accumbens DA depletions, it has been suggested that accumbens DA participates in the sensorimotor/motivational processes that enable organisms to overcome response constraints (8,9, 50–53,58). As noted in a recent review (53), it is possible that accumbens DA depletions make demand for food less elastic in terms of work-related response costs.

The results described above indicate that injections of 6-OHDA into the core had substantial behavioral effects, whereas shell injections produced little or no change in operant responding. Of course, the interpretation of these findings must be tempered by the pattern of neurochemical depletion shown by each group. Injections of 6-OHDA into the shell were shown to produce substantial depletions in the shell (i.e., about 10% of control levels), and much smaller depletions in the core. Thus, injections of 6-OHDA into the shell produced a relatively selective DA depletion in a particular subregion of accumbens. However, injections of 6-OHDA into the core produced a much more widespread depletion of DA, with substantial reductions in both core and shell DA. This pattern of depletion was shown in all three 6-OHDA experiments. It is uncertain why injections of 6-OHDA into the core resulted in such widespread depletions, while shell injections led to more restricted depletions. This pattern would result if DA fibers pass through the core, or remain in the vicinity of the anterior commissure, before innervating the shell. It is possible that the behavioral impairments were significant in the core 6-OHDA groups because both core and shell were depleted, although it also is possible that the core is the more critical region for producing the behavioral deficits observed in the present studies. Correlational analyses of the FR5 data suggest that the deficits observed in that study were related to depletions of core DA, and not shell DA. Rats with core injections of 6-OHDA had significantly lower levels of core DA than rats with shell injections, and only the rats with core injections of 6-OHDA showed significant behavioral impairments. Nevertheless, correlational analyses also suggest that shell DA may have contributed to the deficits observed in the concurrent FR5/chow feeding study. Future research should employ different lesion parameters to determine if more selective core depletions of DA can be obtained. Although the anatomical basis of the behavioral impairments resulting from core injections of 6-OHDA remains uncertain, it does appear as though substantial depletions of dorsomedial shell DA are not necessarily accompanied by significant behavioral impairments. As noted above, shell injections of 6-OHDA, which resulted in substantial shell depletions of DA, failed to have significant effects on number of responses emitted in any of the experiments. The shell has been suggested to play an important role in "reward" processes (7,24). Pharmacological manipulation of excitatory amino acid receptors in the shell had

profound effects upon food intake (35,36). Thus, it could be expected that a DA depletion in the shell would produce even more substantial behavioral deficits on food reinforced tasks than a depletion in the core. Yet this was not found to be the case. Although other neurotransmitters in the shell are related to food intake (35,36), it seems unlikely that DA in dorsomedial nucleus accumbens shell is uniquely or critically involved in the reinforcement processes that underlie lever pressing for food.

ACKNOWLEDGEMENTS

This research was supported by a grant from the National Science Foundation. Many thanks to Juliet Aberman for her helpful comments.

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