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Ventrolateral Striatal Dopamine Depletions Impair Feeding and Food Handling in Rats

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SALAMONE, J. D., K. MAHAN AND S. ROGERS. *Ventrolateral striatal dopamine depletions impair feeding and food handling in rats.* PHARMACOL BIOCHEM BEHAV **44**(3) 605–610, 1993.—The present study was conducted to characterize the changes in feeding behavior produced by localized depletion of dopamine (DA) in the nucleus accumbens and subregions of the neostriatum in the rat. Food-deprived rats were given at least 2 weeks of training, which consisted of being placed in a Plexiglas box and being given 15–18 g of food for a 30-min session. After the training period, rats received bilateral injections of the neurotoxic agent 6-hydroxydopamine (6-OHDA) into the nucleus accumbens, ventromedial striatum, or ventrolateral striatum. Observations were made in 30-min tests on days 3 and 7 after surgery, and measures were obtained for total food intake, time spent feeding, rate of feeding, and forepaw usage during feeding. The ventrolateral striatum was the only site at which dopamine depletion altered aspects of food intake. Rats with ventrolateral striatal DA depletion had reductions in food intake, decreases in the rate of feeding, and impaired forepaw usage during feeding. Time spent feeding was not significantly affected by DA depletion. Water consumption was significantly reduced by DA depletions in the ventrolateral striatum but not by depletions at other sites. These results indicate that ventrolateral striatal DA depletions decrease food intake by impairment of motor functions necessary for the performance of feeding behavior.

Dopamine Striatum Nucleus accumbens Feeding Motor control

EXTENSIVE depletion of forebrain dopamine (DA) has been shown to cause pronounced decreases in food intake (19,20,34,37). Most studies of dopaminergic involvement in feeding have employed injections of the neurotoxic agent 6-hydroxydopamine (6-OHDA) into the lateral ventricles or medial forebrain bundle (MFB) in the rat, which in general leads to widespread depletions of DA, severe loss of food intake, akinesia, and sensorimotor deficits (19,20,34–37,43,44). Because of the widespread nature of the DA depletions in these studies, the specific roles of different DA terminal regions in feeding behavior remain unclear. Considerable evidence indicates that striatal DA is closely associated with the feeding deficits produced by DA depletion, and the lateral striatum in particular has been implicated in feeding behavior. Depletion of DA in the lateral striatum produces severe sensorimotor deficits (7,9) and feeding deficits (6). Deficits in feeding behavior produced by striatal DA depletions were correlated with DA depletions in the lateral striatum (34). DA depletions in the ventrolateral striatum (VLS), but not the ventromedial or dorsolateral striatum, reduced 24-h food intake (12).

In most cases, investigators used gross indices of food intake, such as 24-h intake or body weight, to measure the impairment produced by DA depletion (12,19,20,36,37). Recently, a detailed behavioral characterization of the effects of DA depletion on food intake in rats was reported (34). Depletion of DA by injection of 6-OHDA into the MFB decreased the amount of food intake and rate of feeding. DA-depleted rats showed impaired forepaw usage during feeding, as measured by a relative decrease in the use of both forepaws to hold the pellets. Over several weeks, DA-depleted rats recovered time spent feeding, and eventually spent more time feeding than control rats, despite persistent decreases in feeding rate. The present study was designed to investigate the involvement of DA terminal regions in feeding behavior by injecting 6-OHDA directly into the VLS, anteroventromedial striatum (AVMS), and nucleus accumbens. The nucleus accumbens was investigated in addition to the striatal sites because this DA terminal region has been implicated in aspects of food motivation (13,15,21,30,31). In the present study, rats were observed in 30-min feeding sessions to study the effects of localized DA depletions on parameters of feeding such as feeding duration, feeding rate, and food handling. Rats were observed on the third and seventh days after surgery because previous results (12) indicated that the feeding deficits produced by local striatal depletions are present only in the first few days after surgery and recover rapidly.

METHOD

Subjects

Subjects were 33 male Sprague-Dawley rats (Harlan-Sprague-Dawley, Indianapolis, IN). Animals were deprived of

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food until they weighed 85% of their free-feeding body weight. Rats were maintained on 15–18 g of lab chow each day. If an animal was unable to eat a sufficient amount of dry food after surgery, it received wet mash, made of regular lab chow, water, and sucrose, to help maintain its target weight. On feeding test days, wet mash was given after the feeding tests were conducted.

Observations

Observations were done using a Plexiglas box (28 × 28 × 28 cm) with a wire mesh floor. Rats were given 30-min sessions in the box when they reached their target weights, with 15–18 g of food (approximately three pellets of lab chow) and a water bottle available. After 2 weeks of initial training, surgery was performed. Observations were made on days 3 and 7 after surgery by an observer unaware of the experimental treatment. Feeding was defined as the presence of chewing behavior that occurred during direct mouth contact with the food pellet or chewing that was initiated during mouth contact with the food pellet but continued uninterrupted after mouth contact with the food has ceased. Rats were observed for time spent feeding in which they held the pellet with two forepaws, and a separate measure was obtained for time spent feeding in which they used one or no forepaws. Electromechanical timers were used to record the behavioral data. Quantities of food (correcting for spillage) and water were measured before and after each session to determine how much had been consumed. Rate of feeding (in g/min) was calculated by dividing the amount of food consumed by the total time spent feeding.

Surgery

Rats were randomly assigned to one of four separate groups: VLS DA depletion (n = 7), AVMS DA depletion (n = 7), nucleus accumbens DA depletion (n = 7), or control injection of the vehicle solution (n = 12, 4 per site). DA depletion was produced by bilateral injection of 10.0 μg 6-OHDA per side into the particular brain region (4.0 μg/μl of the freebase of 6-OHDA in 2.5 μl 0.1% ascorbic acid vehicle solution). Injections were made at the following coordinates: VLS, AP 1.6, ML 4.0, DV −7.2; AVMS, AP 2.2, ML 2.0, DV −6.5; nucleus accumbens, AP 2.8, ML 1.4, DV −7.8. Control injections consisted of 2.5 μl ascorbic acid vehicle, with four rats receiving injections into each of the three placement loci. Solutions were delivered through a stainless steel 30-ga injector connected by PE-10 tubing to a 10-μl syringe. Injections were delivered at a rate of 0.75 μl/min by a Harvard Apparatus (South Natick, MA) syringe pump.

High-Performance Liquid Chromatography Assays for DA

After observations were finished, all animals were decapitated and brains were removed. Brains were frozen on a microtome and 0.6-mm thick coronal sections were cut. A hollow stainless steel tube (16 ga) was used to punch out sections of tissue in the nucleus accumbens, AVMS, and VLS. These samples were placed in 0.1 N perchloric acid and homogenized. The solution was then centrifuged. The supernatant was assayed using high-performance liquid chromatography (HPLC) to determine the level of DA in each of the tissue samples. The HPLC system consisted of a Waters pump (Waters Assoc., Milford, MA), a Rheodyne injector, and an ESA Coulochem electrochemical detector. The mobile phase was a pH 4.5 phosphate buffer with EDTA, sodium octyl sulphate, and 7.0% methanol added.

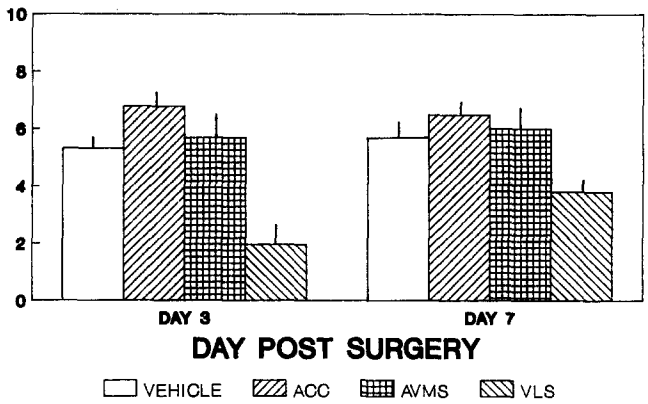

FIG. 1. Mean (±SEM) food intake (g) during the feeding tests on days 3 and 7 after surgery. VEH, vehicle controls; ACC, accumbens dopamine (DA) depletion; AVMS, anteroventromedial striatal DA depletion; VLS, ventrolateral striatal DA depeletion.

Data Analysis

A factorial analysis of variance (ANOVA) with repeated measures on the days factor was used to analyze the data. Parameters examined included amount of food intake, amount of water intake, total time spent feeding, rate of feeding, and percentage of time eating with one or no forepaws (time spent feeding with one or no forepaws divided by total time spent feeding × 100). Analysis of simple main effects (16) was conducted in cases in which there were significant interactions, and the Newman-Keuls test was used for posthoc comparisons. Neurochemical data from tissue assays were analyzed by simple ANOVA for each brain region.

RESULTS

Feeding and Drinking Behavior

Depletion of DA in the VLS significantly reduced food intake (see Fig. 1). ANOVA demonstrated that there was a significant effect of treatment group, $F(3, 29) = 8.8$, $p < 0.05$, a significant effect of test day, $F(1, 29) = 6.6$, $p <$

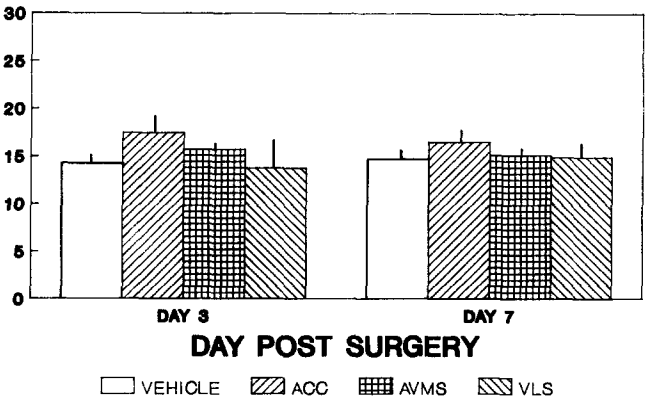

FIG. 2. Mean (±SEM) time spent feeding (min) during the feeding tests on days 3 and 7 after surgery. VEH, vehicle controls; ACC, accumbens dopamine (DA) depletion; AVMS, anteroventromedial striatal DA depletion; VLS, ventrolateral striatal DA depletion.

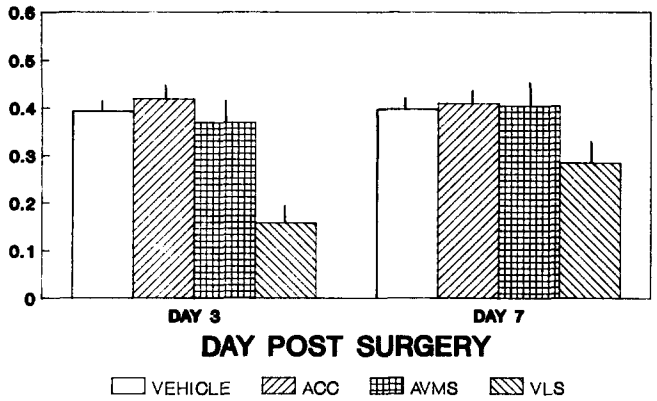

FIG. 3. Mean (±SEM) feeding rate (in g/min) during the feeding tests on days 3 and 7 after surgery. VEH, vehicle controls; ACC, accumbens dopamine (DA) depletion; AVMS, anteroventromedial striatal DA depletion; VLS, ventrolateral striatal DA depletion.

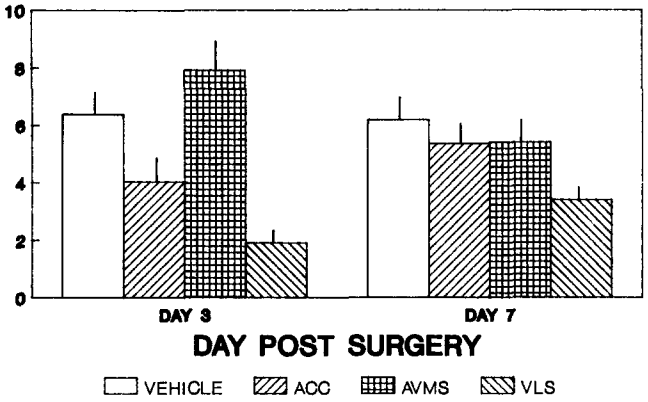

FIG. 5. Mean (±SEM) water intake (ml) during the feeding tests on days 3 and 7 after surgery. VEH, vehicle controls; ACC, accumbens dopamine (DA) depletion; AVMS, anteroventromedial striatal DA depletion; VLS, ventrolateral striatal DA depletion.

0.05, and a significant group × day interaction, $F(3, 29) = 4.4$, $p < 0.05$. Analysis of simple effects demonstrated that there was a significant group effect only on the day 3 test but not on the day 7 test. Newman-Keuls analyses demonstrated that only the VLS group differed from controls on the day 3 test. Analysis of simple effects also indicated that the VLS group showed a significant increase in food intake from days 3–7 after surgery. Despite the effects of DA depletion on food intake, there were no significant effects of 6-OHDA treatment on time spent feeding (Fig. 2). There was not a significant treatment effect, $F(3, 29) = 0.9$, n.s., nor a significant effect of test day, $F(1, 29) = 0.006$, n.s., nor a significant interaction, $F(3, 29) = 0.2$, n.s.

Injection of 6-OHDA into the VLS produced substantial effects on feeding rate (Fig. 3). There was an overall effect of 6-OHDA injection of feeding rate, $F(3, 29) = 5.1$, $p < 0.05$, but no effect of test day and no group × day interaction. Posthoc comparisons indicated that only the group with VLS 6-OHDA injections had significantly lower feeding rates than control rats. Figure 4 shows the effects of regional DA depletion on forepaw usage. There was a significant effect of treatment on feeding with one or no forepaws, $F(3, 29) = 18.2$, a significant effect of test days, $F(1, 29) = 18.9$, and a significant treatment × day interaction, $F(3, 29) = 17.8$. Analysis of simple effects indicated that there was a significant group effect only for the day 3 test and not on day 7 and that the VLS treatment group showed a significant decrease in feeding with one or no forepaws on day 7 compared to day 3. Newman-Keuls analysis indicated that only the VLS group differed from controls during the day 3 test.

VLS DA depletions also reduced water intake (Fig. 5). ANOVA showed that there was an overall effect of 6-OHDA treatment, $F(3, 29) = 7.08$, $p < 0.01$, but no significant effect of test day, $F(1, 29) = .013$, n.s., and no significant group × day interaction, $F(3, 29) = 2.7$, n.s. Posthoc comparisons showed that only the VLS group had significant reductions in water intake.

Analyses of Tissue Samples

The results of HPLC analyses of tissue samples are shown in Table 1 (locations of each brain region are depicted in Fig.

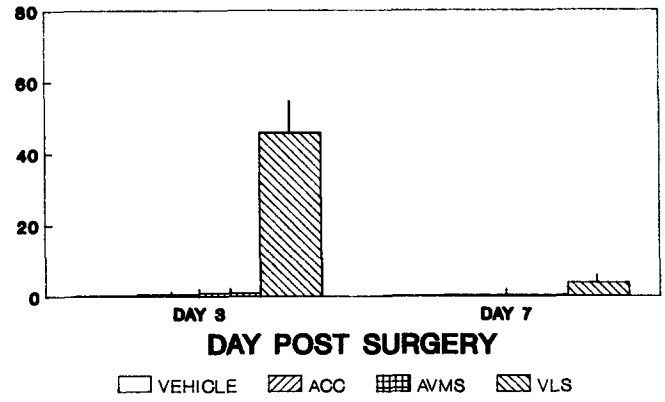

FIG. 4. Mean (±SEM) % time feeding without both forepaws; forepaw usage during the feeding tests on days 3 and 7 after surgery. VEH, vehicle controls; ACC, accumbens dopamine (DA) depletion; AVMS, anteroventromedial striatal DA depletion; VLS, ventrolateral striatal DA depletion.

TABLE 1

DA LEVELS (ng DA/mg TISSUE) FROM TISSUE SAMPLES OF THE NUCLEUS ACCUMBENS, ANTEROVENTROMEDIAL, AND VENTROLATERAL STRIATUM IN VEHICLE- AND 6-OHDA-TREATED RATS

	Treatment Group			
Brain Region	Control	ACC	AVMS	VLS
Nucleus accumbens				
Mean	8.22	2.34*	4.29*	7.34
SEM				
AVMS				
Mean	11.47	7.95	2.68*	9.79
SEM				
VLS				
Mean	11.62	10.16	13.53	3.38*
SEM				

*$p < 0.05$ compared to control group.

6). There was a significant overall effect on tissue levels of accumbens DA, $F(3, 29) = 15.29$, $p < 0.01$. Posthoc comparisons showed that DA in the nucleus accumbens was significantly reduced by injections of 6-OHDA into the nucleus accumbens and AVMS. There was a significant effect of treatment group on DA levels in the AVMS, $F(3, 29) = 18.4$, $p < 0.01$, and posthoc analyses showed that only injection of 6-OHDA into the AVMS significantly reduced DA levels in the AVMS. There was a significant effect of treatment group on DA levels in the VLS, $F(3, 29) = 19.33$, $p < 0.01$, and posthoc analyses showed that only injection of 6-OHDA into the VLS significantly reduced DA levels in VLS tissue samples.

General Observations

Rats with VLS DA depletions were observed to have several difficulties with aspects of food intake. These rats shifted the position of the food pellet frequently with their forepaws rather than holding it still. In addition, VLS-depleted rats were seen to scrape the food pellets with their teeth and take small nibbles off the sides of the food pellets. Typically, the partially eaten food pellets left by VLS-depleted rats had unusual and irregular shapes compared to those left by normal rats. In general, it appeared that the highly organized and coordinated execution of oral and forepaw control characteristic of feeding in rats was disrupted by VLS DA depletion. Although rats with VLS DA depletions had difficulty eating lab chow pellets, all could maintain their body weight by consumption of wet mash.

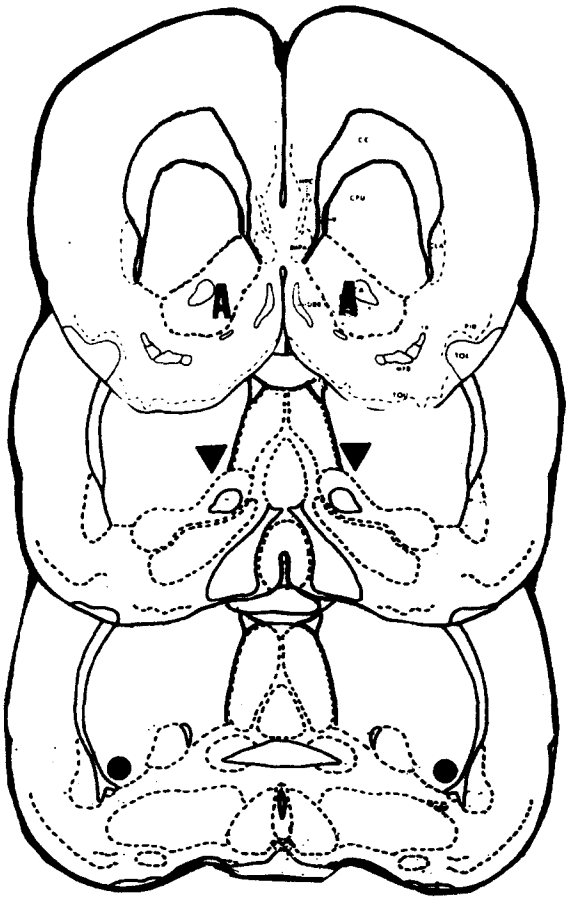

FIG. 6. Locations of injections sites for the nucleus accumbens (A), anteroventromedial striatum (▼), and ventrolateral striatum (●).

DISCUSSION

Depletions of DA in the VLS impaired feeding behavior, whereas DA depletions in the nucleus accumbens and AVMS were ineffective. These results are consistent with a growing body of evidence indicating that the lateral striatum, especially the VLS, is important for the control of feeding behavior. Injections of 6-OHDA into the lateral striatum reduced food intake (6), and deficits in feeding rate produced by forebrain DA depletion were correlated with DA depletion in the lateral but not the medial striatum (34). Food intake deficits in rats with large DA-depleting lesions were correlated with changes in single-cell firing in the lateral but not the medial striatum (24). It was recently reported that the VLS was the only region in which DA depletion reduced 24-h food intake (12). Injections of haloperidol directly into the VLS reduced feeding, and other injection sites were shown to be ineffective (2). VLS lesions produced by injections of ibotenic acid were shown to reduce food intake and feeding rate (25). In the present study, rats with VLS DA depletions spent normal amounts of time feeding but showed impairments in feeding rate and food handling. These data are consistent with the hypothesis that the VLS is involved in motor or sensorimotor functions necessary for normal feeding behavior.

Recovery of function was shown in animals that had VLS DA depletions. This finding is consistent with several previous reports of recovery of feeding after large forebrain DA depletions (34,36,42–44). Compared to the extended recovery shown in the aftermath of extensive DA depletions, the recovery that followed local injections of 6-OHDA in the VLS were relatively rapid. In a previous study of 24-h food intake (12), it was also reported that feeding recovered within the first 7 days after surgery in rats that received VLS injections of 6-OHDA. This rapid recovery of feeding behavior after focal 6-OHDA injection [present study; see also (12)] could be due to the fact that the VLS DA depletions produced in these experiments (71–75%) were not as substantial or widespread as the depletions typically produced by 6-OHDA injected into the medial forebrain bundle. The DA depletions obtained using the present methods are comparable to some experiments that used local injection of 6-OHDA (28) but smaller than those reported in other studies (8). In the present experiment, the rat that had the greatest VLS DA depletion also showed the smallest recovery of feeding rate. Thus, it is possible that the degree of DA depletion and severity of the initial deficit are related to the rate of recovery. In addition, it is possible that DA from nearby terminals diffuses into the areas of the focal DA depletion, which could mean that a slight increase in postsynaptic DA receptors in the depleted area is enough to restore some degree of motor function.

Nucleus accumbens DA depletions had no significant effect on any parameter of food intake, consistent with previous reports showing that global indices of food intake are not reduced by depletion of accumbens DA (15,17,37,40). Injections of haloperidol directly into the nucleus accumbens did not decrease food intake and in fact produced slight increases in feeding (2). Nucleus accumbens DA is important for spontaneous and drug-induced locomotor activity (17,18). Several studies have demonstrated that motor activities induced by

periodic food presentation are reduced by injections of 6-OHDA into the nucleus accumbens (21,23,27). Periodic food presentation (1 45-mg food pellet every 45 s) produced significant increases in accumbens DA release, although presentation of large quantities of food that elicited food consumption produced only small, nonsignificant changes in DA release (21). Thus, it appears that accumbens DA is involved in the induction of activities produced by periodic food presentation, and in instrumental responses for food such as lever pressing (30,31,33), but has less involvement in food consumption per se.

In the present study, the VLS was the striatal subregion in which DA depletions were most effective in impairing feeding behavior. Previous research has demonstrated that 24-h food intake was decreased by DA depletion in the VLS but not by depletions in the AVMS or dorsolateral striatum (12). In addition, deficits in feeding were correlated with DA depletion in the VLS but not the AVMS or dorsolateral striatum (12). Yet, despite these results indicating that dorsolateral striatal DA depletions did not affect food intake there is evidence that the dorsolateral striatum is involved in forepaw motor control and feeding behavior (25). Future research should focus on identifying the precise region within the lateral striatum in which DA depletions affect forepaw control.

Rats with VLS DA depletions attempted to feed and spent normal amounts of time feeding. In terms of gross measures of motor activity, DA depletions in the VLS do not produce akinesia and have not been shown to impair locomotor activity or rearing behavior (12). The deficit in food intake produced by VLS DA depletion was related to specific aspects of the motor responses involved in food consumption. Feeding rate was substantially reduced in rats with VLS DA depletions. This was consistent with several previous reports indicating that interfering with DA systems by DA antagonist drugs or DA depletion primarily affects feeding rate or efficiency (3,5,34). Rats with VLS DA depletions in the present study showed impaired forepaw usage during feeding, similar to the effects reported to occur after haloperidol injection or widespread forebrain DA depletion (29,34). In addition, rats with VLS DA depletions had reductions in water intake, and it was observed that these rats showed some problems with biting and sometimes scraped the lab chow with their teeth. Together, these results are consistent with the notion that the VLS is important for forepaw and oral motor control. These behavioral deficits produced by VLS DA depletion could be related to impairments in the execution of motor acts, problems with the coordination or temporal organization of oral and forepaw movements, or impairments in sensorimotor function.

The present results support the notion that the neostriatum of the rat has functionally distinct subregions. Evidence indicates that the functional heterogeneity of the striatum may be related to the different anatomic inputs of each subregion. The sensorimotor cortex in the rat projects to the lateral striatum (4,22,38,41). Evidence indicates that lateral striatum of the rat, like the putamen of primates, may be organized in a somatotopic manner (1,26). In the rat, there is evidence for a ventral/dorsal gradient, with orofacial regions represented in the more ventral regions of the lateral striatum and more caudal regions of the body represented in progressively more dorsal areas of the lateral striatum (22,26). Thus, the ability of VLS DA depletions to disrupt feeding behavior could be related to a loss of DA in parts of the lateral striatum involved in regulating oral and forepaw motor control. This suggestion is consistent with studies showing that the VLS is important for the production of oral movements (12,14,15,32) and that DA depletions or striatal lesions in the vicinity of the VLS can disrupt forepaw reaching (8,26,28,39). These data from the rat also are consistent with the suggestion that the basal ganglia of primates are involved in the control of distal musculature (11).

ACKNOWLEDGEMENTS

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