Dopaminergic regulation of feeding behavior: II. Differential effects of amphetamine microinfusion into three striatal subregions

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This study examined the involvement of intrastriatal dopaminergic mechanisms on feeding and spontaneous locomotor activity in food-deprived (19 h) rats. In three separate experiments, amphetamine (0, 1, 10, and 20 $\mu\text{g}/0.5 \mu\text{l}$) was bilaterally infused into the nucleus accumbens (N.Acc.), the ventrolateral striatum (VLS), or the dorsolateral striatum (DLS). Administration of the higher doses of amphetamine into both the N.Acc. and the VLS reduced feeding. However, the overall profiles of behavior suggested different underlying mechanisms. Treatment of the DLS did not appear to influence ingestive behaviors. Locomotor activity and oral stereotypy were differentially affected by drug infusion into the three sites. The data suggest that dopamine transmission in the N.Acc. may be important for attentional mechanisms that regulate the temporal distribution of competing behaviors. In contrast, the VLS appears to mediate oral motor functions that are critical for feeding. The DLS appears to be minimally involved in regulating either behavior.

The investigation of neural substrates of appetitive behaviors has been a major field of research for many decades. Early theories proposed the existence of dual hypothalamic centers for hunger and satiety (Anand & Brobeck, 1951; Hetherington & Ranson, 1939). These theories were later rejected on the basis of evidence that hypothalamic lesions could also sever other fibers and generally disrupt many processes in addition to feeding (Gold, 1973; Gold, Jones, Sawchenko, & Kapatos, 1977; Marshall, Richardson, & Teitelbaum, 1974; Stricker, 1982; Teitelbaum & Epstein, 1962; Ungerstedt, 1971). More recent studies have shown that central dopaminergic pathways are important in the mediation of different types of ingestive behaviors. Nonregulatory feeding, which is elicited in sated animals by nonspecific stimuli such as noise, light, handling, mild shock, drugs, tailpinch, and electrical brain stimulation, is thought to involve both the nigrostriatal and the mesolimbic dopaminergic systems (Antelman, Rowland, & Fisher, 1976; Antelman & Szechtman, 1975; Antelman, Szechtman, Chin, & Fisher, 1975; Mittleman, Castaneda, Robinson, & Valenstein, 1986; Mogenson & Wu, 1982; Robbins & Fray, 1980). It is sometimes hypothesized that nonregulatory feeding reflects a response to stress. Adjunctive behaviors, which are often oral in nature, are similar in appearance to the consummatory responses triggered by nonspecific stimuli. Although the exact mechanism underlying these behaviors is not known, it is thought that various stressful stimuli may in-

duce a release of dopamine that elicits feeding. As a tool for investigating the role of dopamine transmission in alimentary behaviors, researchers have utilized amphetamine, which functions as a dopamine releaser and weak reuptake inhibitor.

Amphetamine has historically been considered an anorectic agent in humans. However, the process through which it suppresses appetite is not yet fully understood. Paradoxical effects on feeding have been attributed to amphetamine, which, when administered to animals, acts as a stimulant at low doses and a suppressant at higher ones (Colle & Wise, 1988b). This phenomenon has sometimes been explained by the "inverted U" theory of amphetamine arousal. This argument proposes the existence of an optimal level of dopaminergic activation (Heffner, Zigmond, & Stricker, 1977; Zigmond, Heffner, & Stricker, 1980) and suggests that deviations from this level result in alterations in behaviors such as feeding. Low doses of amphetamine may lead to a maximum state of activation and enhance ingestive behavior, as might nonspecific stressful stimuli. Higher doses may produce a state of "overarousal," in which increased motor behaviors predominate and interfere with the ability to feed.

Various other theories have been proposed to account for both the anorectic and the stimulating properties of amphetamine. It is not known if amphetamine-induced decreases in consummatory behaviors are due to a specific reduction in appetite or result from behavioral competition due to motor hyperactivity, or are caused by some combination of both processes. It has also been suggested that amphetamine may exert changes in feeding patterns by affecting macronutrient selection; several studies have found that amphetamine treatment caused rats to selectively decrease their intake of proteins (Blundell &

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Rogers, 1980; Leibowitz, Shor-Posner, Maclow, & Grinker, 1986).

However, as mentioned above, amphetamine is also able to increase feeding. It was observed that low doses augment food intake in sated rats (Blundell & Latham, 1978). This facilitative effect has been noted in food-deprived rats as well (Colle & Wise, 1988b). Furthermore, Colle and Wise (1988a) reported that low doses of amphetamine enhance nonregulatory feeding that is elicited by lateral hypothalamic stimulation. One proposed mechanism for these augmentations is that amphetamine acts by increasing the rewarding nature of stimuli such as food, which in turn leads to an increase in consumption (Evans & Eikelboom, 1987).

The main purpose of the present investigation was to examine the process through which amphetamine, when injected into selected regions of the forebrain dopamine system, affects feeding in food-deprived animals. Much of the previous work in the feeding literature has reported the effects of systemic injections. However, it is likely that certain discrete sites might regulate different aspects of feeding, based on their putative roles in motivated and oral behaviors in general. We employed the intracranial microinjection technique to isolate and examine the involvement of specific striatal regions. In addition, a microanalysis of feeding was used. This procedure allows the analysis of distinct aspects of feeding behaviors so that a complete profile of ingestive behavior can be obtained (Blundell, 1987).

The sites selected for study were the nucleus accumbens (N.Acc.), the ventrolateral striatum (VLS), and the dorsolateral striatum (DLS). Traditionally, two major classes of function have been ascribed to the N.Acc.: the regulation of motivational or hedonic states (Fibiger & Phillips, 1986; Stellar & Stellar, 1985) and the control of spontaneous motor activity (Iversen, 1977; Koob, Stinus, & LeMoal, 1981). It has also been proposed that this structure is the interface between the limbic and the motor systems and is thus involved in the translation of motivational states into actions (Mogenson, Jones, & Yim, 1980). In addition, it has previously been shown that feeding behaviors can lead to increased dopamine release and metabolism in the N.Acc. (Blackburn, Phillips, Jakubovich, & Fibiger, 1986; Heffner, Hartman, & Seiden, 1980; Radhakishun, van Ree, & Westerink, 1988). Because motivational and motor processes and their interaction are integral components of consummatory behaviors, the effects of amphetamine infusion into the N.Acc. were examined.

The VLS was selected for its putative role in consummatory behaviors and oral motor performance. In sated animals, low doses of amphetamine infused into this region result in a slight enhancement of food intake. High doses induce intense, perseverative stereotypies of an oral nature that are often performed to the exclusion of all other behaviors (Kelley, Gauthier, & Lang, 1989; Kelley, Lang, & Gauthier, 1988). In the present study, the effects of dopaminergic stimulation of this region were examined

in food-deprived animals, which are naturally motivated to feed. It was hypothesized that because of the importance of oral motor mechanisms in coordinating the physical aspects of feeding, pharmacological manipulation of the VLS would result in alterations in feeding.

Finally, the DLS was chosen as the intermediate site between the two others to determine the anatomical specificity of behavioral effects. This region receives afferents from forebrain motor areas that control limb and postural movements (Kelley, Domesick, & Nauta, 1982). Previous work from this laboratory has suggested that dopaminergic stimulation of this region does not alter oral behavior or motor activity (Kelley et al., 1989; Kelley et al., 1988).

METHOD

Subjects

Eight male Sprague-Dawley rats (Charles River) weighing 300–350 g were used in each of three experiments, for a total of 24 rats. Animals were maintained individually in clear plastic cages with wire grid floors and were kept on a 12:12-h light:dark cycle with lights on at 0800 h. They were given access to food *ad lib* (Agway Rat Chow) and water. Food was removed 19 h prior to each testing session and replaced immediately after the session.

Surgical Procedures

Rats were anesthetized with sodium chloral hydrate (60 mg/ml, initial dose 1.3 ml). They were secured in a Kopf stereotaxic apparatus and bilateral stainless steel cannulae guides (23-ga) were implanted at the appropriate sites, which are described below. Coordinates were determined on the basis of the atlas of Pellegrino and Cushman (1967). For implantation in the N.Acc., the coordinates were 3.5 mm anterior to bregma, 1.7 mm lateral to the midline, and 5.7 mm ventral from the skull. The coordinates for the VLS were 2.0 mm anterior to bregma, 4.0 mm lateral to the midline, and 4.7 mm ventral from the skull. The coordinates for the DLS were 2.7 mm anterior to bregma, 3.0 mm lateral to the midline, and 3.4 mm ventral from the skull. Guide cannulae were affixed to the skull with light-curable dental resin. Wire stylets were inserted into the guide cannulae to prevent occlusion. Animals were allowed a recovery period of 3 days before behavioral testing.

Microinjections and Drug Preparation

Bilateral injection cannulae (30-ga) were lowered through the skull cannulae to the site being studied. For the N.Acc. and ventrolateral striatal infusions, injection cannulae were lowered 2.5 mm beyond the guide cannulae tip, reaching to 8.2 and 7.2 mm below the skull, respectively. For the dorsolateral striatal infusions, injection cannulae were lowered 1.5 mm beyond the guide cannulae, reaching to 4.9 mm below the skull. The injection cannulae were connected via polyethylene tubing to a microdrive pump (Harvard Apparatus), which delivered the drug over a 93-sec session. A volume of 0.5 μ l of solution was administered to each side. After drug infusion, a 1-min diffusion period was allowed before removal of the needles and replacement of the stylets. All drugs were dissolved in Hanks's balanced salt solution (Whittaker Bioproducts). One preliminary injection of vehicle was carried out, before all experimental testing, to adapt the rats to the microinjection procedure. Each experiment consisted of 4 test days, which were separated by intervals of 1 day. Three experiments were conducted in which D-amphetamine (Sigma Chemicals) was injected into one of the three sites. The doses of amphetamine were 1, 10, and 20 μ g. All doses are given as the amount dissolved in 0.5 μ l of Hanks's solution. For each experiment, the three drug doses and a vehicle

treatment were counterbalanced for order, so that each rat served as its own control.

Behavioral Testing

The rats were habituated to the observation room for 2 h on the day prior to testing. A sheet of blank white paper was placed beneath each cage grid to familiarize the rats with its presence during testing. Experimentation was carried out between 1100 and 1500 h. Immediately prior to injection, the paper was placed under the cage grid to catch spilled food. Animals were injected and placed back into their home cages. Cages were brought into the testing room, and four food pellets (normal Agway chow) were scattered along the cage grid. Behavioral monitoring began immediately after food dispersal and replacement of the cage lid. An event recorder linked to a Eurobeeb microcomputer (Paul Fray, Ltd, Cambridge, U.K.) was used continuously throughout the 30-min session to measure spontaneous motor and ingestive behaviors. The following parameters were recorded: locomotion (crossing over cage center), feeding, and drinking. The frequency, total duration (in seconds), and mean duration (in seconds) of these behaviors were recorded, except for locomotion, for which only frequency was recorded. The frequency for feeding and drinking was termed "number of bouts" (the number of times an animal either picked up food and commenced feeding or started drinking). Latencies to initiate feeding and drinking were also recorded. The mean duration of a behavior was calculated as the total duration (in seconds) divided by the frequency. Feeding rate (total food ingested divided by total feeding time, resulting in a measure of grams/minute), total food ingested (grams), and total food spilled (grams) during the trial were calculated after the test session. The measure of total food ingested did not include the amount of food that had been spilled. A time-sampling procedure was also used to note stereotypic behaviors. These behaviors were recorded every 5 min for a 1-min observation period. The observer entered a 1 for the presence of a certain behavior and a 0 for its absence. The scores were totaled over the 30-min session to obtain a stereotypy score. The monitored behaviors were biting, sniffing with head up, sniffing with head down, gnawing directed at self, and licking. At all times, the observer was blind to pharmacological treatment.

Histology

After completion of the test days, rats were deeply anesthetized with Nembutal and perfused transcardially with isotonic saline followed by 10% formalin. The brains were removed and stored in 10% formalin for a few days, after which they were frozen with dry ice and cut into 60- μ m sections. The slices were mounted, defatted and stained with cresyl violet. Sections were examined under a microprojector to determine the accuracy of the cannulae placement.

Data Analysis

The data were analyzed by using a Wilcoxon signed-ranks test for comparison between means. Since multiple comparisons between means were made, a Bonferroni adjustment procedure was applied to determine the acceptable level of significance. For every parameter analyzed, a total of three comparisons were carried out; therefore, the conventional alpha level of $p < .05$ was divided by three, resulting in an alpha level of $p < .02$. To be considered statistically significant, p values had to be less than .02.

RESULTS

Spontaneous Motor Behavior

Figure 1 illustrates the effects of amphetamine on locomotor activity. In rats receiving injections into the N.Acc., amphetamine elicited a dose-dependent increase in locomotor activity that was statistically significant for the 10- μ g ($p < .009$, Wilcoxon signed ranks) and 20- μ g ($p < .006$) doses. Amphetamine infusion into the VLS did not significantly influence locomotor activity. A small effect was noted following administration of the highest dose into the DLS ($p < .013$), compared with vehicle. However, it is clear from Figure 1 that amphetamine was considerably less potent as a locomotor stimulant in the DLS than in the N.Acc. After injection into the N.Acc., the high dose of amphetamine produced approximately

Figure 1. Effects of amphetamine infusion into striatal regions on locomotor activity. N.Acc. = nucleus accumbens; VLS = ventrolateral striatum; DLS = dorsolateral striatum. * $p < .02$, $\dagger p < .01$.

Figure 2. Effects of amphetamine infusion into striatal regions on food intake. N.Acc. = nucleus accumbens; VLS = ventrolateral striatum; DLS = dorsolateral striatum. * $p < .01$.

a fivefold increase in locomotor counts compared with the vehicle score, whereas administration of the same dose into the DLS resulted in a twofold increase of locomotor counts.

Ingestive Behaviors

Figure 2 presents the effects of drug treatment on total food intake. A dose-dependent attenuation of food intake that was statistically significant for the 20- μ g dose ($p < .006$) was observed following amphetamine administration into the N.Acc. Food intake was also diminished by amphetamine infusion into the VLS. Following administration of the two higher doses into the VLS, 7 out of 8 rats showed lower intake scores than they showed after vehicle infusion. The effect approached sig-

nificance for the 10- μ g dose ($p < .062$) and was statistically significant at the 20- μ g dose ($p < .009$). No parameter of feeding behavior was altered by amphetamine infusion into the DLS.

A similar profile was seen for the total duration of feeding (Figure 3). A decrease in overall feeding time resulted after amphetamine infusion into both the N.Acc. and the VLS. Both the 10- μ g ($p < .034$) and the 20- μ g ($p < .006$) doses inhibited feeding duration after infusion into both sites.

Table 1 presents other observed measures of feeding. Average duration of a feeding bout was decreased by drug administration into both the N.Acc. and the VLS. The 20- μ g dose produced the attenuation ($p < .009$) when it was infused into the N.Acc. Both the medium and the high

Figure 3. Effects of amphetamine infusion into striatal regions on total time spent on feeding. N.Acc. = nucleus accumbens; VLS = ventrolateral striatum; DLS = dorsolateral striatum. * $p < .01$.

Table 1
Effect of Amphetamine Infusion into Striatal Subregions on Other Feeding Parameters

Treatment	Feeding Bouts		Mean Bout Duration (sec)		Spillage (g)		Feeding Rate (g/min)		Median Latency to Initiate Feeding (sec)
	M	SEM	M	SEM	M	SEM	M	SEM	
N.Acc. (n = 8)									
Vehicle	23	1	40	4	0.80	0.13	0.32	0.02	51
1 μ g Amph	30	4	24	4	0.82	0.21	0.39	0.04	60
10 μ g Amph	27	4	26	9	0.93	0.27	0.65*	0.06	54
20 μ g Amph	22	4	12*	3	0.46	0.07	0.65*	0.06	54
VLS (n = 8)									
Vehicle	27	3	36	4	1.16	0.26	0.31	0.02	49
1 μ g Amph	25	4	43	6	1.04	0.17	0.29	0.03	57
10 μ g Amph	27	3	23†	5	1.21	0.30	0.52	0.14	77
20 μ g Amph	34	4	14†	3	2.44	0.57	0.70*	0.18	93
DLS (n = 8)									
Vehicle	12	1	81	16	0.70	0.14	0.29	0.05	67
1 μ g Amph	14	2	103	35	0.70	0.06	0.26	0.01	68
10 μ g Amph	14	2	70	15	0.69	0.20	0.31	0.03	89
20 μ g Amph	15	2	61	6	0.74	0.08	0.29	0.01	51

Note—N.Acc. = nucleus accumbens; VLS = ventrolateral striatum; DLS = dorsolateral striatum; Amph = amphetamine. All parameters shown, except for latency to initiate feeding, represent the mean $\pm$ SEM for each treatment. Median latencies were calculated for the latency to initiate feeding because of the large variation in values within any treatment. * $p < .02$; † $p < .01$.

doses shortened bout duration when they were infused into the VLS ($p < .009$).

Feeding rate was also affected by amphetamine stimulation of both the N.Acc. and the VLS, as is seen in Table 1. An enhancement in feeding rate was observed after treatment with both the 10- μ g ($p < .018$) and the 20- μ g ($p < .009$) doses infused into the N.Acc. Feeding-rate values following treatment with these doses were nearly double those that followed treatment with vehicle.

Feeding rate was also elevated by injection of the highest dose of amphetamine into the VLS ($p < .018$).

An interesting effect was noted when we examined the food spilled during the test session. Amphetamine stimulation of the VLS tended to cause rats to spill more food as they ate. Although this trend did not reach statistical significance according to the present method of analysis ($p < .046$), it is important to note that infusion of the 20- μ g dose nearly doubled the amount of food spilled com-

Table 2
Effect of Amphetamine Infusion into Striatal Subregions on Drinking Parameters

Treatment	Drinking Bouts		Total Duration (sec)		Mean Bout Duration (sec)		Median Latency to Initiate Drinking (sec)
	<i>M</i>	<i>SEM</i>	<i>M</i>	<i>SEM</i>	<i>M</i>	<i>SEM</i>	
N.Acc. (<i>n</i> = 8)							
Vehicle	9.6	1.9	172	20	25	7	551
1 μ g Amph	10.3	3.1	102	16	13	2	579
10 μ g Amph	8.3	3.6	80	32	6†	2	1,661†
20 μ g Amph	3.1*	1.9	38	22†	6*	4	1,800*
VLS (<i>n</i> = 8)							
Vehicle	4.6	0.7	163	21	40	7	527
1 μ g Amph	5.1	1.1	139	23	28	7	562
10 μ g Amph	3.3*	0.8	129	24	59	23	806
20 μ g Amph	7.0	2.3	112	24	26	10	1,058
DLS (<i>n</i> = 8)							
Vehicle	3.0	1.5	147	42	49	17	1,143
1 μ g Amph	3.6	0.9	136	32	36	7	576
10 μ g Amph	3.4	0.9	85	20	25	6	951
20 μ g Amph	4.6	0.8	187	36	39	7	588

Note—N.Acc. = nucleus accumbens; VLS = ventrolateral striatum; DLS = dorsolateral striatum; Amph = amphetamine. All parameters shown, except for latency to initiate drinking, represent the mean $\pm$ SEM for each treatment. Median latencies were calculated for the latency to initiate drinking because several animals did not drink. The highest possible latency, 1,800 sec, was assigned to these animals. * $p < .02$; † $p < .01$.

pared with the value following vehicle infusion. In contrast, food spillage tended to *decrease* after amphetamine treatment of the N.Acc. ($p < .062$).

There was a trend, which did not reach significance, toward a prolonged latency to initiate feeding following injection of the highest amphetamine dose into the VLS ($p < .034$). This parameter was not affected by drug administration into the other two sites. The number of feeding bouts was not significantly affected by treatment in any of the sites.

Table 2 provides the effects of amphetamine treatment on drinking behaviors. The total number of drinking bouts was significantly reduced by infusion of the 10- μ g dose ($p < .009$) and the 20- μ g dose ($p < .013$) into the N.Acc. A similar effect was observed after administration of the medium dose into the VLS ($p < .013$). A reduction in the total time spent on drinking was also noted after injection of the 20- μ g dose into the N.Acc. ($p < .009$). No effects were observed for any parameter of drinking following drug infusion into the DLS.

A decrease in the average duration of a drinking bout was noted following administration of the 20- μ g dose ($p < .02$) and the 10- μ g dose ($p < .009$) into the N.Acc. No alterations in this parameter of drinking were observed after treatment of the other two sites.

The median latency to initiate drinking was increased by amphetamine injection into the N.Acc. and VLS. A strong effect was noted following administration of both the 10- μ g dose ($p < .009$) and the 20- μ g dose ($p < .013$) into the N.Acc., but the trend did not reach statistical significance following injections into the VLS.

Figure 4 shows the effects of amphetamine infusion into the VLS on oral stereotypy scores. Oral stereotypy scores were significantly greater than control scores following

infusion of the high dose ($p < .017$). The 10- μ g dose also increased stereotypy, although not quite significantly ($p < .030$). Amphetamine injections into the N.Acc. or the DLS did not induce oral stereotypy.

In addition to the oral stereotypy, an unusual activity was informally noted in some of the rats that were injected with the two higher doses of amphetamine into the VLS. It was observed that they engaged in a perseverative series of movements, which consisted of their grasping the food pellets in both front paws and then twirling them around several times. Some rats concurrently scraped the pellets with their teeth, often letting food drop out of their mouths. Usually, they exhibited this behavior for an uninterrupted period of several minutes. The phenomenon was not recorded as feeding because the pellets did not appear to be chewed and ingested. Rather, the behavior appeared to be an oral stereotypy that was directed toward the food.

Histology

Histological analysis revealed that all cannulae placements were properly situated in the desired regions. A visual representation of the data is provided in Figure 4 of our companion article (Bakshi & Kelley, 1991, p. 223).

DISCUSSION

The present results support the theory of a functionally heterogeneous striatum with respect to ingestive and motor behaviors. Feeding behavior was disrupted following amphetamine infusion into the N.Acc. The animals also showed large increases in motor behavior. Pharmacological manipulation of the VLS did not alter motor activity, but it did affect consummatory responses. Although food intake was attenuated following treatment of both the N.Acc. and the VLS, close analysis of the data suggests different underlying mechanisms. Treatment of the DLS did not systematically alter any index of ingestive behaviors, indicating that this region is not critically involved in consummatory responses.

Nucleus Accumbens

Following infusion of the 20- μ g dose of amphetamine into the N.Acc., food intake and total feeding duration were significantly decreased. Concurrent increases in locomotor activity were seen. This behavioral profile suggests that injections of high doses of amphetamine into the N.Acc. result in a general activation that causes animals to depart from consummatory responses and engage in other competing behaviors such as locomotion. Dopaminergic stimulation of the N.Acc. has been traditionally known to elicit spontaneous motor activity (Jackson, Anden, & Dahlstrom, 1975), and decreases in food intake resulting from behavioral competition have previously been documented in mildly food-deprived animals that received intraaccumbens amphetamine injections (Carr & White, 1986; Evans & Vaccarino, 1986). Our

Figure 4. Effects of amphetamine infusion into the ventrolateral striatum on oral stereotypy. Stereotypy scores represent the mean number of observation periods during which stereotypy occurred. * $p < .02$.

data are in agreement with these previous findings and also suggest a possible mechanism underlying the behavioral competition.

It is hypothesized that the infusion of high doses of amphetamine into the N.Acc. creates an inability to normally distribute time among several competing behaviors. It was noted that the administration of the 20- μ g dose significantly shortened the average duration of a feeding bout. However, no changes were observed in the frequency of feeding bouts or in feeding-onset time. This behavioral profile suggests that amphetamine-treated animals are able to approach and acquire food as often and as rapidly as controls, but that once feeding has begun, animals prematurely terminate ingestive behaviors to engage in locomotor activity. Blundell and Latham (1980) also noted fragmented feeding activity interspersed with locomotion following the systemic administration of amphetamine.

Drinking behavior was also affected by amphetamine infusion into the N.Acc. Frequency, total duration, and average duration of drinking bouts were reduced following administration of the highest doses. The latency to initiate drinking was concurrently lengthened by drug treatment. These data indicate that amphetamine-treated animals drank later and less frequently than those treated with vehicle. Furthermore, individual drinking bouts were prematurely terminated, as indicated by shortened mean bout duration. This profile is consistent with the observed disruption of feeding activity and further supports the theory that the injection of high doses of amphetamine into the N.Acc. impair an animal's ability to maintain its focus on ingestive behaviors.

It has previously been proposed that dopaminergic transmission in the N.Acc. is critical for switching from one type of behavior to another (Robbins & Koob, 1980). Lesions of this region can alter the pattern of time allocation among ingestive and locomotor responses (Koob, Riley, Smith, & Robbins, 1978; Robbins & Koob, 1980). Data from our accompanying study suggest that dopaminergic blockade of this region significantly prolongs an animal's focus on feeding, resulting in elevated feeding durations and food intake (Bakshi & Kelley, 1991). It thus appears that a certain optimal level of dopaminergic transmission in the N.Acc. is critical for the regulation of attentional mechanisms that are necessary for normal feeding.

Some researchers have proposed that in mildly food-deprived animals, amphetamine treatment may increase the hedonic impact of environmental stimuli and thus decrease the relative prepotent rewarding capacity of natural reinforcers such as food (Carr & White, 1986). Although this may be possible in mildly food-deprived animals, it does not seem to be the case with strongly deprived ones. If the rewarding nature of food were relatively lessened, animals might be expected to approach food less often and later and perhaps feed more slowly than they normally would. However, in the present study, no changes in the frequency or the latency to initiate feeding were observed. In addition, feeding rate was enhanced

by amphetamine treatment. Although the present study does not directly address this question, the data suggest that the relative reinforcing potential of food does not diminish following infusion of amphetamine into the N.Acc. in stringently food-deprived animals.

Ventrolateral Striatum

Although decreases in ingestive behaviors were also noted following amphetamine infusion into the VLS, examination of the microcomponents of feeding suggest a different underlying mechanism. Unlike the N.Acc., the VLS does not seem to be involved in attentional mechanisms that mediate the distribution of behaviors. The mean duration of feeding bouts was also decreased following infusion of the higher doses into the VLS. However, observation of the profile of other behaviors suggests that this attenuation was due to the disturbance of oral motor mechanisms. Unlike treatment of the N.Acc., treatment of the VLS did not increase locomotor activity. Nor were total duration, mean duration, and latency to initiate drinking significantly affected. These data suggest that rats that received amphetamine injections into the VLS were able to properly execute switching from feeding to other behaviors, achieving the normal balance between feeding, drinking, and locomotor activity that is exhibited by vehicle-treated animals.

The deficit in feeding observed after administration of the two higher doses of amphetamine into this site can be alternatively explained in terms of a disruption of oral motor performance. The index of oral stereotypy was significantly increased by administration of both the 10- μ g and the 20- μ g doses. Stereotypy was characterized by intense, perseverative bouts of gnawing, licking, and biting that were often directed at the forelimbs or cage. Performance of these behaviors is incompatible with feeding, and it is thus likely that the induction of intense oral stereotypy was responsible for the decrease in feeding.

It was further noted that the *manner* in which the animals fed was markedly affected by the infusion of the medium and high doses of amphetamine into the VLS. Amphetamine-treated animals appeared to feed in a frenzied manner, constantly biting off more of the food pellet before they had completely chewed or swallowed the previous mouthful. Also, following administration of the 20- μ g dose, rats spilled nearly twice the amount of food that they spilled after treatment with vehicle. Feeding rate was also approximately doubled after treatment with this dose. The data indicate that rats began to feed rapidly and inefficiently after treatment with the high amphetamine doses. Furthermore, stereotypy was often directed toward the food, with the rats grasping, twirling, and biting the food without ingesting it.

Thus, the behavioral profile of these animals suggests that several aspects of normal feeding can be disrupted by the infusion of high doses of amphetamine into the VLS. The high incidence of oral stereotypy, food spillage, and accelerated feeding rate can account for the observed overall decreases in time spent on feeding and food

intake. The data indicate that the VLS may regulate feeding behavior by mediating the oral motor responses that are necessary for normal feeding.

Previous studies have shown that the infusion of high doses of amphetamine into this site results in the induction of strong oral stereotypies in sated animals (Kelley et al., 1989; Kelley et al., 1988). It has been found that these rats engage in licking, biting, and gnawing behaviors to the exclusion of all other activity, achieving an average stereotypy score of 4.0. The stereotypy scores of animals in the present study were approximately half of this value, suggesting that food deprivation can affect the extent to which oral stereotypy is induced. It appeared that the animals in the present study exhibited a behavioral profile that is intermediate between that of a food-deprived, vehicle-treated animal, which almost exclusively feeds, and that of a sated, amphetamine-treated animal, which engages in oral stereotypy to the exclusion of other behaviors.

Dorsolateral Striatum

Infusion of the 20- μ g dose of amphetamine into the DLS produced a relatively mild but significant enhancement in locomotor activity. It is possible that, considering the proximity of the DLS and the N.Acc., this effect was caused by some diffusion of amphetamine into the N.Acc. Alternatively, since the DLS is thought to be involved in sensory-motor integration (Fairley & Marshall, 1986; Joyce & Van Hartesveldt, 1984; Pisa, 1988), direct stimulation of this region may result in mild motor arousal. Amphetamine treatment of this site did not significantly alter any indexes of feeding or drinking behaviors. It thus seems that the DLS is minimally involved in ingestive behaviors.

It may be noted that the vehicle baseline for locomotor activity was slightly lower for the DLS group compared with the other two sites. We have noted lower baselines for a number of behaviors in this cannulation group (see also Bakshi & Kelley, 1991), which may be caused by tissue damage resulting from the lowering of cannulae through cortical or striatal regions that are critical for sensory-motor processes.

GENERAL DISCUSSION

It is well established (although the mechanisms are not well understood) that amphetamine can both stimulate and suppress feeding behavior. Some researchers have found that intraaccumbens injections of amphetamine can increase feeding at low doses (Colle & Wise, 1988b; Evans & Vaccarino, 1986). Similar effects have been noted following infusion into regions of the striatum (Kelley et al., 1989; Winn, Williams, & Herberg, 1982). It may at first appear that these findings are somewhat inconsistent with the present data, because in this study, no facilitative effect on feeding was observed after amphetamine infusion into any of the three striatal sites. However, many complex variables are able to influence food intake. The site

of injection, dose of amphetamine, food palatability, and amount of food deprivation prior to testing are all critical factors. Much variation in methodology exists within the feeding literature, so that direct comparisons are difficult to make. In all of the above studies that found increases in feeding in response to low doses of amphetamine, animals were either sated or only mildly deprived of food prior to testing. Yet there is evidence for a significant interaction between amphetamine effects and level of food deprivation (Cole, 1979). Doses of amphetamine that do not affect food intake in sated animals do significantly inhibit food intake in the same animals when they are deprived of food for 12 or more hours. Discrepancies between our data and previously reported augmentations in feeding may thus be caused by the more stringent level of deprivation in our animals. An example of the importance of level of food deprivation is provided by the fact that in sated animals, low doses of amphetamine infused into the VLS actually enhance feeding, rather than inhibit it (Kelley et al., 1989). Thus, within the same site, opposite effects may be obtained, depending on both dose and level of deprivation.

Results from the present study may help to explain the possible roles that different striatal subregions play in amphetamine anorexia in food-deprived animals. The N.Acc. seems to subserve attentional mechanisms that govern how time is distributed among feeding and other behaviors. Infusion of high doses of amphetamine into this region disturb this process and cause an animal to shift away from feeding very often, which should be the activity made predominant by deprivation. In contrast, amphetamine infusion into the VLS appears to disrupt oral motor mechanisms that are necessary for the normal execution of feeding responses.

Other studies have investigated the involvement of different brain regions and neurotransmitters in the regulation of ingestive behaviors (Blundell, 1987; Blundell & Latham, 1980; Evans & Vaccarino, 1990; Fletcher, 1987; Fletcher & Davies, 1990; Leibowitz, 1975; Samanin et al., 1979). Normal feeding may depend on interactions between several brain regions and neurotransmitter systems. Thus, a disturbance of any one of these factors may be sufficient to disrupt intact feeding. Additional work, and particularly the use of both intracerebral microinjection and microanalysis of feeding, can be valuable in the further pursuit of this complex question.

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