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Striatal Dopaminergic Modulation of Lateral Hypothalamic Self-Stimulation

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NEILL, D. B., S. D. PARKER AND M. S. GOLD. *Striatal dopaminergic modulation of lateral hypothalamic self-stimulation.* PHARMAC. BIOCHEM. BEHAV. 3(3) 485–491, 1975. – The bilateral application of crystalline 6-hydroxydopamine to the ventral anterior head of the corpus striatum of rats severely suppressed responding for electrical stimulation of the lateral hypothalamus. This suppression lasted for days or weeks, after other behavioral deficits in food and water intake and activity had recovered. Application of crystalline dopamine through the same cannulas temporarily reversed the impairment. Applications of crystalline dopamine to the same striatal region of untreated rats were more effective in enhancing self-stimulation than similar applications of norepinephrine.

Reinforcement Self-stimulation Corpus striatum 6-Hydroxydopamine Dopamine Norepinephrine

THE concept of reinforcement is central to much of psychological theory. Knowledge of the neural mechanisms mediating reinforcement would greatly enhance our understanding of the brain processes involved in learning. A significant advance in methods to investigate the neural correlates of reinforcement occurred in 1954, when Olds and Milner [26] reported that rats would bar press (self-stimulate) for electrical stimulation of some brain sites. These results suggested that it might be possible to directly examine the neural substrates of positive reinforcement. Anatomical mapping studies [19,27] have generally agreed that intracranial self-stimulation is strongest at points along the medial forebrain bundle (MFB) which connects brainstem and forebrain. The demonstrations [2,18] that the MFB contains neurons which utilize specific neurotransmitters have suggested that this reinforcement mechanism might be chemically specific. Numerous pharmacological studies [3, 8, 14, 34] have indicated that the critical transmitter for self-stimulation is a catecholamine. Many investigators [3, 14, 31, 34, 35, 42] have suggested that norepinephrine (NE) is involved in this behavior.

Some recent evidence, however, has indicated that dopamine (DA) might also be involved, because (1) high rates of self-stimulation can be obtained from ventral midbrain points where the dopaminergic contributions to the MFB originate [11, 19, 32], (2) pharmacological impairments of dopaminergic transmission suppress hypothalamic self-stimulation [9,22], sometimes more than similar impairments of noradrenergic transmission [9,23], and (3) differential systemic drug effects on self-stimulation in dopaminergic and noradrenergic brain areas have been observed [29].

The largest brain dopaminergic system appears to be that of the nigrostriatal bundle [38], extending from the substantia nigra of the ventral midbrain to the corpus striatum (caudate and putamen) of the forebrain. We examined the role of this dopaminergic system in the maintenance of lateral hypothalamic self-stimulation by assessing the effects of intrastriatal applications of 6-hydroxydopamine (6-OHDA) on this behavior. Centrally administered 6-OHDA has been reported [6,37] to not only deplete nerve terminals of catecholamines but to permanently damage them as well, resulting in a chemically specific biochemical lesion. Intraventricular injections of this drug suppress hypothalamic self-stimulation [5,36]. In our experiments, we also measured spontaneous food and water intake and locomotor activity to determine if the behavioral effects of the 6-OHDA were specific to self-stimulation or nonspecifically involved many behaviors.

Some investigators [30] have suggested that injections of 6-OHDA may exert their behavioral effects by producing nonspecific neural damage. Having a chronic cannula in place through which the applied 6-OHDA might suppress responding opened the possibility of a novel test of whether nonspecific damage was entirely involved. Some studies [4, 17, 43] have reported that behavioral changes following the

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depletion of specific central neurotransmitters can be ameliorated by exogenous repletion of the transmitters. With regard to self-stimulation, Saint-Laurent *et al.* [33] found that systemic injections of apomorphine, which directly stimulates dopamine receptors, partially restored hypothalamic self-stimulation which had been suppressed by alpha-methyl-para-tyrosine.

We attempted to reverse our self-stimulation impairment by directly applying dopamine through the same cannulas through which 6-OHDA had earlier been applied to suppress responding. Although the pre-synaptic terminals were presumably destroyed by the 6-OHDA, the post-synaptic receptors should still be present and may be supersensitive [39].

Finally, we examined the effect of direct catecholaminergic stimulation of the ventral anterior striatum on hypothalamic self-stimulation in rats which had not been previously treated with 6-OHDA or any other drug. This was done to examine whether self-stimulation could be enhanced by this treatment without prior 6-OHDA, and whether DA and NE might show different relative potencies.

METHOD

Animals

Twenty male CFE albino rats (Carworth, Portage, Michigan) weighing 350–400 g at surgery were used. All were individually housed with food and water available ad lib. Colony lights were on from 9 a.m. – 9 p.m. and all testing was performed in the afternoon..

Apparatus

Self-stimulation rates were measured in a single-lever operant conditioning chamber equipped with a mercury commutator. Electrical stimulation (100 pps, 1 msec monophasic pulses, constant current) was delivered to the hypothalamic electrode for 0.3 sec after each bar press. Spontaneous activity was measured in a 47 X 47 X 46 cm chamber containing sixteen 10 cm^2 aluminum plates mounted 1 cm apart at the edges; contact between two plates was detected by a touch-detector circuit and automatically recorded. An air blower on the top of the chamber provided a masking noise.

Procedure

Surgery. All surgery was performed under sodium pentobarbital anesthesia (50 mg/kg) using a Kopf stereotaxic device. Double-walled stainless steel cannulae (outer: 22 ga; inner: 30 ga) were bilaterally implanted at the various brain sites. A unilateral bipolar stainless steel electrode was simultaneously placed in the lateral hypothalamus and the entire assembly secured to the skull with dental cement.

Using the atlas of Pellegrino and Cushman [28], the cannulae were aimed at the ventral (n = 7) or dorsal (n = 4) portion of the anterior striatum (in front of the junction of the anterior commissure). These two striatal sites were chosen on the basis of earlier work [25] indicating functional differences between them. An additional two animals received bilateral lateral septal cannulae. The hypothalamic electrodes were aimed at AP 5.4, H – 2.5, L 1.6.

Behavioral testing. All testing began at least one week after surgery. The animals were given 20 min tests of spontaneous activity or 15 min self-stimulation tests on alternate days 6 days a week. Stimulus intensities were individually set for each animal to maintain a rate of 700–1000 responses per 15 min session and ranged from 100–250 μA. Food (Purina Lab Chow) and water intake and body weight were monitored daily throughout the experiment.

After at least three consecutive days of stable (± 10 percent) self-stimulation rates were obtained, approximately 20 μg (determined on a microbalance) of crystalline 6-hydroxydopamine hydrobromide (Regis Chem. Co., Chicago, Ill.) was tamped into each inner cannula, which was replaced in the animals' heads 20 hr before the next self-stimulation session. The inner cannulae remained in the animals for the next 3 weeks of continuous testing.

Five of the 7 rats with ventral striatal cannulae were used to examine the possibility that application of DA through the cannulae might reverse the deficit caused by 6-OHDA. One month after the 6-OHDA application, 4 of these rats still would not respond for hypothalamic stimulation; the fifth had recovered to approximately 60 percent of its predrug rate. The inner cannulae were removed, cleaned, and returned to the animals' heads for a 15 min self-stimulation test. Immediately after this test, the cannulae were again removed but loaded with approximately 20 μg of crystalline dopamine HCL (Sigma Chem. Co.) before placing the animals in the test chamber.

The relative effects of DA and NE applications in rats which had not received 6-OHDA were tested using 7 rats with ventral anterior striatal cannulas and LH electrodes. After initial training to bar-press for hypothalamic stimulation, a current level was determined for each animal which would maintain low rates of responding (150–200 responses per 15 min test). Current intensities for this test ranged from 15 to 30 μA.

After a few days of testing at the low current levels, drug applications began. The animals were placed in the chamber and allowed to respond for 15 min while responses were recorded every 15 min. Both inner cannulae were then removed, cleaned, and loaded with approximately 20 μg of crystalline dopamine HCL (Sigma), norepinephrine HCL (Sigma), or nothing (sham condition). The inner cannulae were then replaced in the animals' heads and responding was recorded every 5 min for 30 min. Drug order varied between animals.

Although responding was recorded in 5 min blocks, the first 5 min after drug application were not considered because of the possible activating effects of handling the animal for the application. Since drug effects became clearly evident 10–15 min after application, the last 15 min of the 30 min postdrug test were analyzed. The variable of interest was the difference between the responses in the last 15 min of the postdrug interval and responses in the 15 min test preceding drug application.

Histology. After all tests were completed, the rats were given a lethal dose of pentobarbital and intracardially perfused with isotonic saline followed by 10 percent Formalin. Later, 50 micron thick frozen sections were taken through the regions of the cannula and electrode tips and stained with cresyl violet.

Evaluation of results. The initial effects of 6-OHDA applications on the various behavioral measures were evaluated using the repeated measures analysis of variance [40]. If the overall analysis was significant ($p<0.05$), group means were compared using the Newman-Keuls test [40].

TABLE 1

SELF-STIMULATION, FOOD AND WATER INTAKE, AND LOCOMOTOR ACTIVITY (± S.E.M.) BEFORE AND AFTER A SINGLE INTRACEREBRAL APPLICATION OF 6-OHDA. FOOD AND WATER INTAKES FOR THE 24 HR AFTER DRUG ADMINISTRATION. SELF-STIMULATION RATE 20 HR AFTER DRUG APPLICATION. LOCOMOTOR ACTIVITY TESTS TWO DAYS AFTER DRUG ADMINISTRATION.

		Self-stimulation (responses/15 min)		Food Intake (gm)		Water Intake (ml)		Activity (20 min test)	
Group	N	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Ventral Striatals	7	1044 ± 53	4 ± 3*	24.6 ± 1.3	6.1 ± 1.5*	40 ± 4	7 ± 3*	330 ± 36	83 ± 18*
Dorsal Striatals	4	861 ± 104	900 ± 128	21.0 ± 1.2	23.6 ± 1.8	38 ± 2	36 ± 3	297 ± 40	261 ± 37
Septals	2	593 ± 231	690 ± 310	26.0 ± 2.8	33.4 ± 2.4	42 ± 3	31 ± 2	342 ± 11	293 ± 6

*$p<0.01$, compared to pre-drug

DA and NE effects on self-stimulation in animals which had not been pretreated with 6-OHDA were analyzed in terms of the absolute change from baseline using a single-factor analysis of variance followed by Newman-Keuls tests [40].

RESULTS

6-OHDA Effects on Self-stimulation

Twenty hours after intrastriatal 6-OHDA applications, the animals with ventral striatal placements were hypoactive, hypophagic, and hypodipsic, and showed little reaction to the manual delivery of electrical stimulation to the hypothalamus (see Table 1). Over the next 10 days (see Fig. 1) food and water intake and spontaneous activity returned to predrug levels. Self-stimulation, on the other hand, recovered more slowly, and in a number of cases (4/7) was completely abolished despite repeated manual priming but was not maintained by the animal.

The animals with dorsal striatal or septal placements did not show any reliable changes on any of the behavioral measures (see Table 1), suggesting that the effective striatal region was anatomically discrete and that the drug did not diffuse throughout the brain to produce its effects.

Effect of DA Applications after 6-OHDA Treatment

In every case (see Table 2), dopamine, when applied through the same cannulas through which 6-OHDA had earlier been applied to suppress responding, dramatically enhanced responding within 10–15 min of its application, even in animals which had not self-stimulated for weeks. The first sign of the dopamine action was increased locomotion accompanied by sniffing, which was often followed by gnawing. These symptoms were similar to those reported by other investigators to follow intrastriatal dopamine injection [10,16]. In some cases the animals began to self-stimulate by themselves; in other cases experimenter-delivered priming stimulation was necessary to start responding. Regardless of how the responding was initiated, the important effect of the dopamine was to develop steady, excited responding.

Catecholamine Applications Without Prior 6-OHDA Treatment

As shown in Table 3, both norepinephrine (NE) and dopamine (DA) reliably ($p<0.05$ and $p<0.01$, respectively) elevated responding for hypothalamic stimulation relative to sham injections. Dopamine was also more potent than a similar quantity of NE ($p<0.01$). The drug-induced enhancement of responding was signaled by the onset of excited sniffing and vigorous responding. These changes in behavior began about 10 min after drug application and were quite obvious 15 min after application.

Histology

Examination of the histological materials (see Fig. 2) showed the cannula tips to be located near the intended sites. Hypothalamic electrode tips were in the posterolateral hypothalamus; their placements were not sufficiently different to readily correlate with the individual differences in duration of drug effects as shown in Fig. 1. Microscopic examination of the brains of the present and other (see [24]) animals did not reveal any damage outside a narrow band of necrotic tissue at the cannula tips, and most sections only showed small black deposits not larger than the cannula diameter.

DISCUSSION

The pattern of results from these experiments suggests that dopaminergic neurotransmission in the ventral anterior striatum is somehow involved in the neural mechanisms of reinforcement as measured by self-stimulation. First, an impairment of catecholaminergic function in this region of the striatum by the direct application of crystalline 6-hydroxydopamine produced a long-lasting suppression of hypothalamic self-stimulation. Although the amount of 6-OHDA applied in these experiments was rather high, a number of observations suggest that it does not diffuse very far when using crystalline applications: (1) we observed little effect on any of our measures for septal and dorsal striatal placements which were as close or closer to the cerebral ventricles as the ventral striatal cannulae; (2) assays

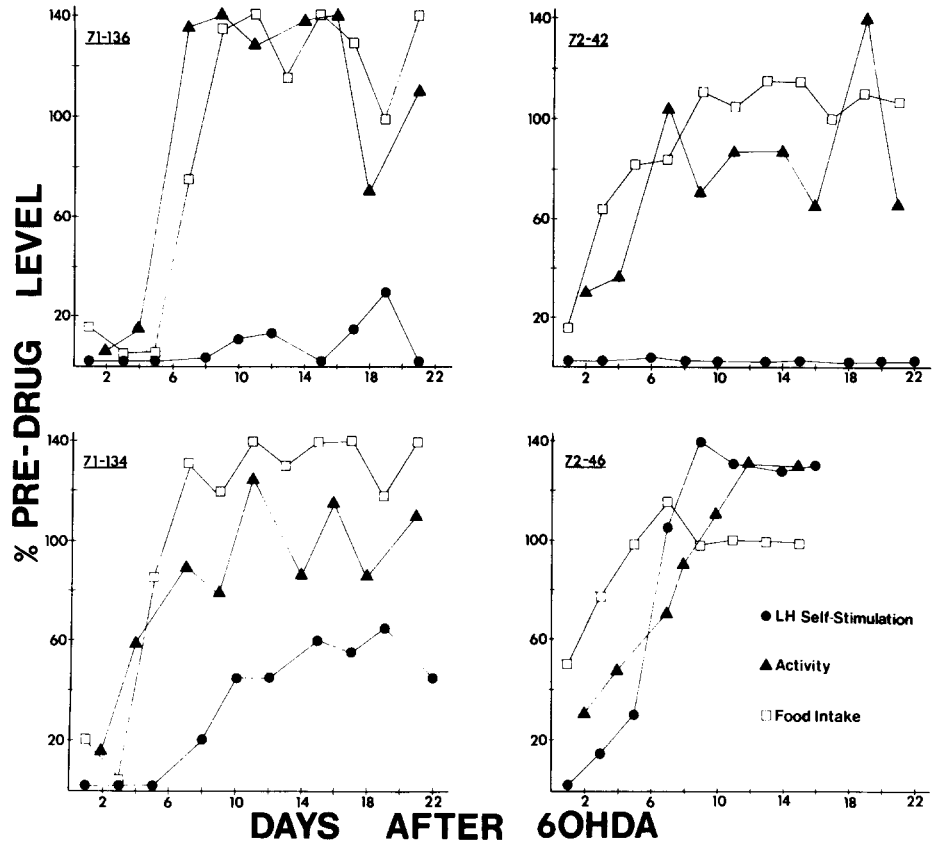

FIG. 1. Representative recovery curves showing minimal (Nos. 136, 42), moderate (No. 134), and complete (No. 46) recovery of self-stimulation after intrastriatal 6-OHDA.

TABLE 2

DOPAMINE ACTIVATION OF SELF-STIMULATION 30 DAYS AFTER ITS SUPPRESSION BY INTRASTRIATALLY APPLIED 6-OHDA

	Responses/15 min test	
Animals	Sham Injection	'Dopamine
71–134	499	631
71–135	69	1000
71–137	0	917
72–42	0	805
72–45	0	760

TABLE 3

AVERAGE RESPONSES (± S.E.M.)/15 MIN FOR LATERAL HYPOTHALAMIC STIMULATION BEFORE AND AFTER THE APPLICATION OF CRYSTALLINE DRUGS TO THE VENTRAL ANTERIOR STRIATUM. RESPONDING IN DRUG AND SHAM CONDITIONS WAS MEASURED FOR THE 15 MIN INTERVAL BEGINNING 15 MIN AFTER INJECTION.

	Total Responses/15 min		
Injection	Pre-drug	Post-drug	Δ
Sham	178 ± 20	136 ± 30	–42 ± 26
Norepinephrine HCl	119 ± 12	171 ± 20	+53 ± 27*
Dopamine HCl	155 ± 17	452 ± 38	+297 ± 43†

*$p<0.05$ compared to sham
†$p<0.01$ compared to sham and NE

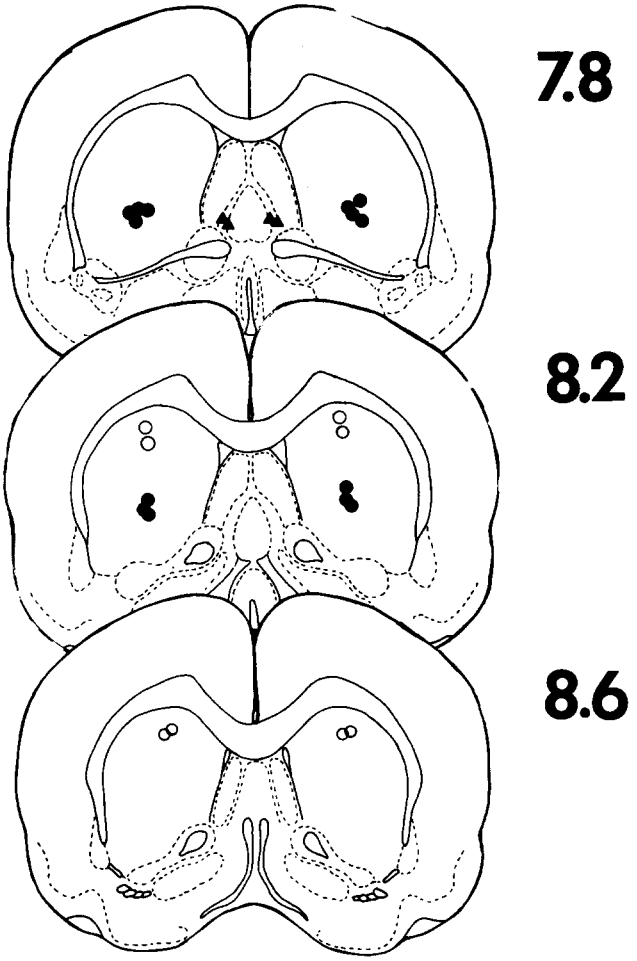

FIG. 2. Anatomical locations [28] of ventral striatal (solid circles), dorsal striatal (empty circles), and lateral septal (triangles) cannula tips for rats receiving intracerebral 6-OHDA.

of forebrain catecholamines after similar applications of even larger amounts of 6-OHDA to the ventral anterior striatum have revealed selective depletions of forebrain dopamine, sparing norepinephrine [24]. Since most forebrain dopamine is in the striatum, this depletion probably reflected striatal dopamine depletion; (3) we have found that using applications of crystalline 6-OHDA to the substantia nigra the behavioral effects varied according to the placement of the cannula within the structure (Neill, Tabor and Chafin, in preparation). This anatomical specificity is unlike that obtained with injections of liquid solutions of 6-OHDA, which although dependent on volume, appear to disperse rather widely [1]. The probable reason for this anatomical specificity is that much of the crystalline drug oxidizes before it can travel far from the cannula tip. We have noticed that much of our crystalline 6-OHDA turns into the black gummy oxidized form while still in the cannula tip and remains there as a plug. So, although anatomical specificity may be more easily obtained with the crystalline applications when compared with the liquid method, the determination of the amount of drug actually reaching the brain is compromised.

The observation that spontaneous consummatory behaviors and activity recovered before self-stimulation suggests some behavioral specificity. The lack of effect of similar amounts of 6-OHDA applied to the dorsal anterior striatum or lateral septum indicates some anatomical specificity.

Second, the finding that the suppression of self-stimulation was temporarily reversed by the subsequent application of dopamine through the same cannulae provides further support for a catecholaminergic involvement. Finally, since applications of dopamine to this area in rats without prior 6-OHDA treatment reliably enhanced self-stimulation responding, 6-OHDA pretreatment is not necessary for the DA effects; since DA was more potent than NE, a predominantly dopaminergic mechanism may be involved. While some of the DA effect could have been due to its intracerebral conversion into NE, this hypothesis cannot account for the comparatively weak effect of direct NE applications.

Other experimental results, while not individually conclusive, are also consistent with the idea of a striatal dopaminergic involvement in reinforcement from hypothalamic stimulation. High rates of self-stimulation are obtained from the substantia nigra, origin of most striatal dopaminergic axons [11, 19, 32]. Phillips and Fibiger [29] have suggested that this nigral stimulation effect is dopaminergic because of the relative potencies of d- and l-amphetamine in increasing responding for such stimulation. Levine *et al.* [21] reported that rats would bar-press for stimulation of the globus pallidus. Recently, it has been found that lesions at some hypothalamic self-stimulation sites result in a pile-up of catecholamine fluorescence in fibers which originate in the substantia nigra [7]. Finally, using a retractable brain knife, Kent and Grossman [20] found that transecting laterally-directed connections of the hypothalamus severely attenuated bar-pressing or alley running for brain stimulation reward. The nigrostriatal dopamine system was probably transected by these cuts as it turned laterally into the globus pallidus.

Disruptions of striatal dopaminergic transmission have also impaired the acquisition and performance of various responses dependent upon more conventional reinforcers. Kent and Grossman [20] reported that after their hypothalamic knife cuts the animals showed much longer than normal latencies in running an alley for a food reward and in a bar-press shock escape paradigm. Fibiger *et al.* [15] have recently shown that rats are markedly subnormal in learning both a simple runway response for food and a shock avoidance task following intranigral injections of 6-OHDA. Zis *et al.* [43] found that this avoidance deficit could be reversed by systemic L-DOPA. The application of 6-OHDA directly to the ventral anterior striatum in amounts which selectively deplete forebrain DA also impairs avoidance performance [24]. At least some of these impairments are apparently not due to decreased motor activity. For instance, Kent and Grossman [20] found their rats to be somewhat hyperactive, and Fibiger *et al.* [15] tested after recovery from the acute general debilitative effects of 6-OHDA.

Our observations of the animals after 6-OHDA suggested to us that the suppression of responding was not simply an inability to perform the motor acts required to bar-press. The animals did not appear as excited by experimenter-applied stimulation as before treatment. If they started responding and left the bar, they usually did not return, and any stimulation-elicited excitement seemed to rapidly

decay. These observations were even more convincing to us in animals that had recovered eating, drinking, and normal levels of spontaneous activity. The most notable change in the bar-pressing behavior of these rats was that if they delayed more than a few seconds between responses, the elicited excitement dissipated and they would typically leave the bar and show some other behavior.

Similarly, we do not believe that the enhancement of responding by DA in rats not receiving 6-OHDA was simply due to a generalized increase in the rate of occurrence of all behaviors. In the usual sham injection test, the animals would often respond in a burst, then walk elsewhere in the chamber to explore or groom, returning to the bar later. After drug applications, and particularly after DA, they would vigorously emit long trains of responding, and if they moved away from the bar they would rapidly return.

An analysis of the behavioral data revealed that the animals which completely recovered self-stimulation (as 72-46 in Fig. 1) also were not as initially impaired on the other behavioral measures as those which did not recover self-stimulation as much. A significant rank-order correlation (rho = 0.89, $df = 6$, $p<0.02$) was found for the ventral placements between the percentage of predrug food intake one day after 6-OHDA and the highest self-stimulation rate reached in the three weeks of postdrug observation. This suggests that some critical degree of catecholamine depletion in the striatum is necessary or considerable recovery of self-stimulation will occur.

It is not surprising that applications of 6-OHDA to the dorsal anterior striatum did not reliably affect any of the behaviors measured. A number of studies with both rats [25,41] and monkeys [13] have shown that different striatal regions are involved in different behavioral functions. Why the ventral anterior region in the rat is particularly important in modulating self-stimulation is a question for future studies.

In conclusion, the evidence from this and other experiments supports the idea that activation of the nigrostriatal dopamine system is involved in hypothalamic self-stimulation. Other evidence, particularly from stimulation in brain areas outside the dopamine tracts [12, 31, 32], supports the idea of another system for self-stimulation which uses norepinephrine as a transmitter. Differences and possible interactions between these two systems are problems for further research.

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