Table 1. Distribution of INA label during the isolation of glycophorin.

Fraction	Percentage of radioactivity when isolated by	
	Lithium diiodosalicylate–phenol	Wheat germ agglutinin–affinity chromatography
Membranes*	100	100
Membranes after dialysis†	60	61
Phenol phase	27	
Material not adsorbed to affinity matrix		53
Glycophorin	10	8

*The membrane preparation contained INA (8.2×10^6 and 5.6×10^6 count/min) for the lithium diiodosalicylate–phenol extraction and the wheat germ agglutinin–affinity chromatography procedure, respectively. †Irradiated membranes were dialyzed for 24 hours at 4°C against 500 ml of 0.05*M* tris-HCl, *p*H 7.4, with bovine serum albumin (2 mg/ml).

tion of about $10^{-6}M$ INA. The suspension was incubated at 37°C for 5 minutes in the dark and then irradiated at 314 nm for 6 minutes (*6*). The suspension was cooled to 4°C, and a sample was withdrawn for sodium dodecyl sulfate (SDS)–polyacrylamide gel electrophoresis (*6*); the rest of the membrane preparation was used to isolate glycophorin. Electrophoretic analysis of the labeled membranes confirmed the observation (*6*) that approximately 20 percent of the INA was covalently attached to the membrane proteins; it was chiefly confined to the regions of band 3, other periodic acid–Schiff–positive bands, and band 7, while very small amounts of label were found in the region of bands 1 and 2 [the numbering system of polypeptide bands is in accord with (*2*)].

Glycophorin that was isolated both by affinity chromatography on wheat germ agglutinin conjugated to Sepharose 4B (*7*) and by lithium diiodosalicylate–phenol (*8*) was highly labeled. The fraction of the radioactivity incorporated into glycophorin was about 10 percent of the total initial radioactivity associated with the membrane (Table 1). Thus, approximately one-half of the [^{125}I]INA attached to the membrane proteins (*6*) resides in glycophorin.

The purified glycophorin was digested with trypsin and the TIS was isolated (*3*). In four separate experiments TIS contained from 80 to 90 percent of the total radioactivity present in glycophorin, almost all of which migrated in SDS–polyacrylamide gel electrophoresis as a broad band typical of TIS (Fig. 1). The other small peak in the TIS fraction was also present in intact glycophorin (Fig. 1); its nature is not known. The proportion of the label incorporated into TIS is probably greater than observed since small amounts of this peptide escape precipitation by the isolation procedure we employed. The radioactivity (less than 10 to 20 percent) not associated with TIS could not be identified as a defined species. It is possible that either some nonspecific labeling by INA takes place or, alternatively, other regions of the protein may have some contact with the lipid bilayer.

The TIS (33 amino acids) represents approximately 25 percent of the glycophorin polypeptide chain and 10 percent of the total molecule (60 percent carbohydrate and 40 percent protein). The finding that it contains between 80 and 90 percent of the radioactivity derived from [^{125}I]INA directly supports the concept that glycophorin is anchored in the lipid backbone of the membrane through its hydrophobic domain (most of TIS) inserted into the lipid bilayer (*3, 4, 9*). These results encourage the use of INA to identify directly segments of other membrane proteins in contact with the lipid bilayer (*5, 6, 10*).

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Kainic Acid Lesions of the Striatum Dissociate Amphetamine and Apomorphine Stereotypy: Similarities to Huntington's Chorea

Abstract. *Kainic acid lesion of cell bodies in the dorsal striatum enhanced the stereotypy-producing effects of* d-*amphetamine without affecting the stereotypy produced by the direct receptor agonist apomorphine. This pattern of results parallels that found in patients suffering from Huntington's chorea, thus strengthening the parallels between the kainic acid animal model and the human disease state initially suggested on biochemical grounds. The present results further suggest a dissociation of the mechanisms involved in the production of stereotypy by these two drugs, perhaps in terms of differential involvement of the striato-nigral negative feedback loop.*

Huntington's chorea is a genetically transmitted autosomal dominant degenerative disease (*1*) characterized by involuntary choreic movements (*2*). Evidence indicates an involvement of the basal ganglia in this disease (*3*), and it has been proposed that rats in which kainic acid has been injected into the striatum provide a model (*4*) that shows considerable biochemical similarities (*5*) to the human disease state. One of the best demonstrated functions of the striatum in animal experiments has been a role in the mediation of the stereotyped behavior patterns (*6*) seen in animals given high doses of the psychomotor stimulant drug amphetamine (*7, 8*). Electrolytic lesion of the entire stratum convincingly blocks amphetamine stereotypy (*9*), as does total destruction of afferent dopamine terminals by means of the selective neurotoxin 6-hydroxydopamine (6-OHDA) (*10*). On the other hand, amphetamine and other dopamine releasing agents, when administered to patients with Huntington's chorea, seem to exacerbate the choreic movements (*11*), that is, they have an enhanced effect compared to an identical dose in normal humans. L-Dopa has, in fact, been suggested to be of use in revealing "presymptomatic" chorea in otherwise apparently normal humans (*12*). Apomorphine, a direct dopamine receptor agonist (*13*), is devoid of this effect (*14*) despite its being highly effective in elicit-

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ing stereotyped behaviors in the rat (*15*).

It would considerably strengthen the parallel with the human disease state if this dissociation of the action of amphetamine and apomorphine could be demonstrated in the kainic acid animal model (*16*). We therefore injected kainic acid, a structural analog of glutamate (*17*), into the striatum of the rat, and examined the stereotypy elicited by various doses of amphetamine and apomorphine. Kainic acid has been shown to damage cell bodies in the striatum while sparing afferent terminals and fibers of passage such as those of the internal capsule (*4, 5*).

Ten male, albino Woodlyn rats, each weighing about 300 g, received bilateral injections of 3 nmole of kainic acid in the striatum (*18*). Ten control rats were injected with the vehicle. The stereotypy induced in these animals by intraperitoneal injections of *d*-amphetamine (5 and 10 mg/kg) and by apomorphine (1, 2, and 4 mg/kg) was rated according to the scale of Kelly *et al.* (*8, 19*). Stereotypy was rated in the home cage every 10 minutes for 2 hours following the intraperitoneal injection of *d*-amphetamine and for 1 hour after injection of apomorphine. Drugs were dissolved in distilled water with, in the case of apomorphine, ascorbic acid (0.3 mg/ml) added to retard oxidation. The mean stereotypy scores in response to amphetamine and apomorphine are shown in Fig. 1. The rats with kainic acid lesions showed a marked and consistent increase in stereotypy in response to amphetamine; however, no alteration occurred in the stereotypy induced by apomorphine (*20*). Both doses of amphetamine produced an enhanced response, whereas none of the three doses of apomorphine produced responses that were significantly affected by the kainic acid lesion (*21*).

Although the peak intensity of the amphetamine stereotypy was increased, its speed of onset was apparently unaltered (Fig. 2). This might be taken to suggest that a negative feedback mechanism, which comes into play to limit the intensity of stereotyped behavior in its most extreme and intense forms, is missing in the animals with kainic acid lesions.

After completion of the behavioral testing, four treated and two control rats were killed and their lesion sites were examined histologically. Frozen sections of brain were cut at 50 μm, and every third section was stained with cresyl violet and counterstained with Luxol blue to reveal cell bodies and fiber bundles, respectively. A typical section through the site of kainic acid injection (Fig. 2) shows considerable damage occurring to cell bodies in the dorsal striatum but significant sparing of the more ventral parts; fiber bundles appear to be completely spared, even in the regions of maximum cell body loss. No damage could be observed in either the adjacent nucleus accumbens or in the cortex overlying the injection site.

A further three treated and three control rats were used for biochemical analysis. The brain of each rat was dissected into striatum, accumbens, and cortical regions and then the striatum was further subdivided by a horizontal and a vertical cut into four quadrants, thus giving a

Table 1. Choline acetyltransferase (CAT), glutamic acid decarboxylase (GAD), and tyrosine hydroxylase (TOH) activities in control and kainic acid–treated rats. The data are expressed in nanomoles per milligram of protein per hour. Values are means of three control and three treated animals (± standard error of the mean).

Area and group	CAT		GAD		TOH	
	Activity	Percentage*	Activity	Percentage*	Activity	Percentage*
Cortex						
Control	23.3 ± 0.57					
Treated	20.6 ± 1.71	88				
Accumbens						
Control	63.7 ± 2.32		62.6 ± 5.95		13.6 ± 0.56	
Treated	58.6 ± 1.54	92	60.3 ± 4.8	97	15.4 ± 0.94	113
Striatal regions						
Dorsomedial						
Control	108.0 ± 5.4		24.8 ± 0.3		26.2 ± 1.0	
Treated	51.3 ± 6.15	47	11.3 ± 2.26	45	23.9 ± 0.15	91
Dorsolateral						
Control	138.6 ± 13.5		27.9 ± 1.65		29.6 ± 0.85	
Treated	94.8 ± 19.5	68	10.4 ± 1.28	37	34.7 ± 0.75	117
Ventromedial						
Control	80.8 ± 1.45		37.0 ± 5.85		26.9 ± 0.75	
Treated	69.1 ± 6.3	86	23.3 ± 6.1	63	30.4 ± 1.35	113
Ventrolateral						
Control	114.5 ± 10.05		32.0 ± 4.5		27.6 ± 1.6	
Treated	115.3 ± 10.85	100	28.0 ± 3.35	88	27.0 ± 2.75	98

*Percentage of control activity remaining in kainic acid–lesioned tissue.

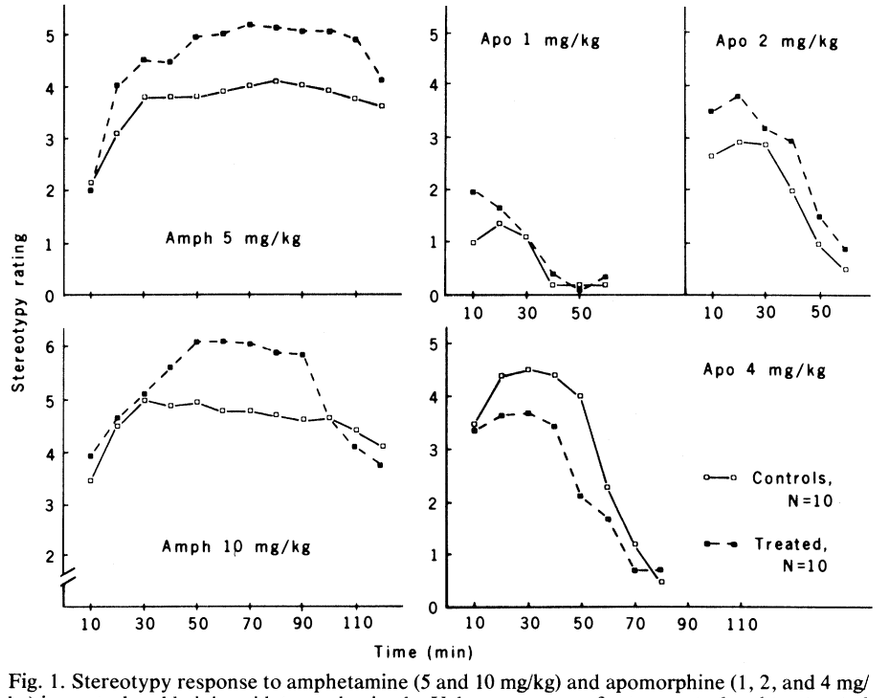

Fig. 1. Stereotypy response to amphetamine (5 and 10 mg/kg) and apomorphine (1, 2, and 4 mg/kg) in control and kainic acid–treated animals. Values are means for ten control and ten treated rats. The stereotypy score, according to the rating scale of Kelly *et al.* (*8*), is plotted against time for 2 hours after the injection of *d*-amphetamine and for 1 hour after the injection of apomorphine.

dorsomedial, dorsolateral, ventromedial, and ventrolateral subarea. These regions were assayed for the activity of the enzymes choline acetyltransferase (E.C. 2.3.1.6) (*22*), glutamate decarboxylase (E.C. 4.1.1.15) (*23*), and tyrosine hydroxylase (E.C. 1.14.16.2) (*24*). The biochemical data (Table 1) agree with the histological examination in showing that the lesion was mainly confined to the dorsal aspect of the striatum with considerable sparing of enzyme activities in the ventral portion and with no alteration in cortex or accumbens. The specificity of kainic acid for cell perikarya is shown by the marked decrease in the dorsal portion of the striatum in those enzymes associated with cells whose soma are intrinsic to the striatum (choline acetyltransferase and glutamate decarboxylase) but with no alteration in the marker enzyme (tyrosine hydroxylase) for the afferent dopamine terminals coming from areas outside the striatum.

The finding that the stereotypy response to amphetamine is increased in rats with kainic acid lesions of the striatum thus parallels that found in Huntington's disease, especially since the apomorphine response is unaltered in both instances. This adds to the previously described biochemical similarities (*5*) between the kainic acid animal model and the human disease state. The consistent increase in the amphetamine response makes the lack of effect on the apomorphine response in the selfsame animals all the more marked.

It is, at first sight, paradoxical that destruction of cell bodies in the striatum should increase amphetamine-induced stereotypy, because destruction of the striatum in other ways usually blocks this stereotypy (*9*, *15*), and lesions made with 6-OHDA, which deplete dopamine in the whole striatum, also attenuate (*25*) or completely block it (*7–9*). The striatum is not a homogenous structure, since smaller lesions (restricted to the ventral part) made electrolytically (*26*) or with 6-OHDA (*27*) are equally effective in blocking amphetamine-induced stereotypy, but lesions made with 6-OHDA in the dorsal striatum (*27*) are without effect and electrolytic lesions of that area increase the amphetamine response (*26*). Similar dissociation of dorsal and ventral striatum is found in the control of active avoidance (*28*), consummatory behavior (*29*), DRL (differential reinforcement of low rate) performance (*30*), and modulation of intracranial self-stimulation (*31*). Thus, our kainic acid lesion, which was restricted to the dorsal aspect of the striatum, is more similar to the electrolytic lesion of Neill *et al.* (*26*), both in location and in terms of increasing the amphetamine response. This suggests that the motor outflow from the striatum that is necessary for the expression of stereotypy, and is damaged by global striatal lesions, may be more restricted to the ventral portion (*27*).

The neuropathology in Huntington's disease may be unevenly distributed through the striatum. One early study repeatedly refers to the "patchy loss" within the caudate (*32*), and a more recent study has clearly characterized a rostromedial area in human choreic caudate as showing the most severe loss of choline acetyltransferase activity (*33*). Although it is not possible anatomically to determine which area of the rat striatum corresponds to the rostromedial portion of the human caudate these results at least suggest that it might be the same dorsal area which was damaged in our studies by kainic acid injections.

On its own, this suggestion fails to explain why an increase in amphetamine-induced stereotypy was observed, rather than no effect, as would be expected by a sparing of the ventral motor outflow. Bunney and Aghajanian (*34*) have found that injections of kainic acid into the striatum, which destroyed cells in this structure and had effect on the more ventral nucleus accumbens, abolished the

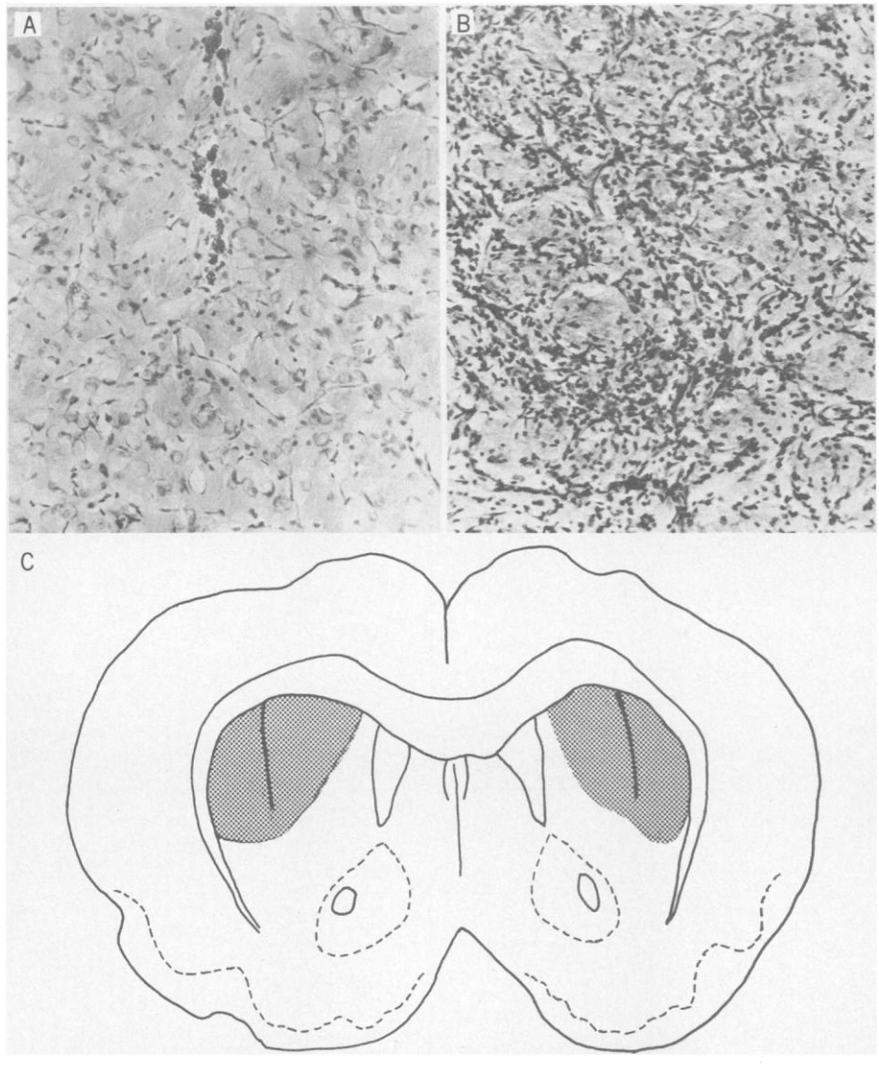

Fig. 2. Section through striatal injection site, stained with cresyl violet and counterstained with Luxol blue. (A) Control animal. (B) Kainic acid–treated animal. The section in (B) shows the marked loss of cell perikarya produced by the lesion and subsequent proliferation of glial cells. In this same area, however, fiber bundles are still intact. (C) Reconstruction of the extent of the lesion. Considerable sparing of the ventral portion of the striatum is evident. Nucleus accumbens and cortex overlying the injection site showed complete sparing of cell bodies, indicating that the lesion did not impinge on these areas. The rostro-caudal extent of the lesion was from approximately A 9650 to A 6570 on the atlas of Konig and Klippel (*18*). No invasion of the globus pallidus was found.

usual inhibition (*35*) of single units in the substantia nigra, pars compacta (SNC), in response to intravenously administered amphetamine. They suggest that the striato-nigral feedback loop (*36–38*) may have been interrupted by the kainic acid lesion. This implies that the effects of amphetamine may be twofold, in that it releases dopamine from the terminals of dopamine neurons in the ventral striatum to cause stereotyped behavior, and inhibits the firing of SNC cells by an action on the striato-nigral feedback loop in the dorsal striatum. Since the amount of dopamine released onto the postsynaptic receptor is known (*39*) to be a combined function of the dose of amphetamine and the electrical activity in SNC neurons, the activation of the postsynaptic receptor in the ventral striatum would be a balance of these two, opposing actions of amphetamine.

Removal of that action of amphetamine which inhibits SNC cells, as may happen after kainic acid lesions have been made in the dorsal striatum, would thus enhance the overall action of amphetamine in releasing dopamine in the ventral striatum to produce the expression of stereotyped behavior. Apomorphine, since it acts directly on the postsynaptic receptor (*13*) would be independent of the release of dopamine from the presynaptic terminal and so would not be affected one way or the other by kainic acid lesion of the dorsal striatum. Thus, disruption of a striato-nigral feedback loop originating in the dorsal striatum may be capable of explaining both the paradoxical potentiation of amphetamine stereotypy and the lack of effect on apomorphine stereotypy.

The kainic acid lesion of the dorsal striatum that we produced in the present animals thus parallels the amphetamine and apomorphine responses found in patients with Huntington's disease, and thus strengthens the view that the animal model is biochemically similar to the human disease states (*4, 5*); it also helps to elucidate the different mechanisms participating in the apparently similar stereotypes produced by amphetamine and apomorphine.

Our data may aid in the endeavor to find a drug treatment for patients with Huntington's disease, in similar vein to the use of L-dopa for Parkinson's disease. Some progress has been made in examining drugs that may restore the biochemical deficiencies of rats with kainic acid lesions (*40*). There is, however, no guarantee that partial restoration of biochemical function will be adequate to restore behavioral normality, and it is practically difficult, as well as of a doubtful ethical nature, to conduct tests on human patients on the basis of such scanty evidence.

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16. The important point is not so much that rat stereotypy should be taken as a model for human choreiform movements, although this has certainly been suggested [R. Rubovits and H. L. Klawans, *Arch. Gen. Psychiatry* **27**, 502 (1972); H. L. Klawens and R. Rubovits, *J. Neural Trans.* **33**, 235 (1972); H. L. Klawans and W. J. Weiner, in *Models of Human Neurological Disease*, H. L. Klawans, Ed. (Excerpta Medica Foundation, Amsterdam, 1975)], but that by duplication of the biochemical changes seen in humans with chorea, through the use of kainic acid injection into the rat striatum, a clear dissociation between the effects of apomorphine and the effects of amphetamine, which is manifest in the human condition, should be seen in a rat species-typical behavior, namely stereotypy.
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18. Three nanomoles of kainic acid were dissolved in 0.5 μl of phosphate buffer, *p*H 7.2, and injected bilaterally via a 34-gauge cannula over a 3-minute period at the following coordinates [from J. F. Konig and R. A. Klippel, *The Rat Brain, A Stereotaxic Atlas* (Williams & Wilkins, Baltimore, 1963)]: AP + 8.8 mm, ML + 2.8 mm, DV + 0.4 mm. After injection the cannula was left in place for a further 5 minutes to allow diffusion of the drug solution. Two weeks were allowed for recovery after the operation before behavioral testing commenced. After a transient hypophagia during the first week after the operation, body weight recovered to control values by the time of initiation of drug testing. Animals were hyperreactive to handling but otherwise appeared similar to controls and remained healthy throughout the duration of testing.
19. A rating of 7 was created to describe stereotyped licking or biting of the animal's own body.
20. A two-factor analysis of variance [B. J. Winer, *Statistical Principles in Experimental Design* (McGraw-Hill, New York, 1962)] with repeated measures on one factor (time) was carried out for each dose of each drug. The *F* ratios were as follows: amphetamine, 10 mg/kg, interaction F (11, 198) = 2.91, $P < .001$; amphetamine, 5 mg/kg, groups F (1, 18) = 4.96, $P < .05$; apomorphine, 1 mg/kg, groups F (1, 18) = 1.76, N.S.: interaction F (5, 90) = 1.69 N.S.; apomorphine, 2 mg/kg, groups F (1, 18) = 1.95, N.S.: interaction F (5, 90) = 0.76 N.S.; apomorphine 4 mg/kg, groups F (1, 18) = 2.08, N.S.: interaction F (7, 176) = 1.75 N.S.
21. Apomorphine and amphetamine were tested on the same animals with the drug order being amphetamine 5, apomorphine 1, apomorphine 2, apomorphine 4, and amphetamine 10 mg/kg. Four drug-free days were allowed between drug administrations.
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38. Some authors have disputed the existence of a striato-nigral feedback loop [P. M. Groves, C. J. Wilson, S. J. Young, G. V. Rebec, *Science* **190**, 522 (1975)] and the feedback inhibition of amphetamine may actually be mediated by release of dopamine within the substantia nigra itself onto dopamine receptors on the terminals of the descending, possibly γ-aminobutyric acid–containing, fibers from the striatum [K. Gale. A. Guidotti, E. Costa, *Science* **195**, 503 (19 → P. F. Spano, M. Trabucchi, G. Di Chiara, *ibid.* **196**, 1343 (1977); C. E. Riback, J. E. Vangh, K. Saits, R. Barber, E. Roberts, *Brain Res.* **116**, 287 (1976)]. These fibers are known to be destroyed after kainic acid lesion of the striatum [E. G. McGeer and P. L. McGeer, *Nature (London)* **263**, 517 (1976)] and so on either mechanism the feedback action would be blocked by such a lesion. Even Groves and co-workers [G. V. Rebec and P. M. Groves, *Neuropharmacology* **14**, 275 (1975)] report that hemitransection of descending fibers from the striatum blocks the usual inhibition of SNC cells to intravenous amphetamine. The location of this effect is somewhat irrelevant to the present findings. The important point is that both Groves and co-workers and Aghajanian and Bunney (*37*) agree that it occurs.
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