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BRIEF COMMUNICATION

Effects of Lesions in the Dorsal or Ventral Striatum on Locomotor Activity and on Locomotor Effects of Amphetamine

DARRYL B. NEILL,[1] JOSEPH F. ROSS, AND SEBASTIAN P. GROSSMAN[2]

Department of Psychology, University of Chicago, Chicago, Illinois 60637

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NEILL, D. B., J. F. ROSS AND S. P. GROSSMAN. *Effects of lesions in the dorsal or ventral striatum on locomotor activity and on locomotor effects of amphetamine.* PHARMAC. BIOCHEM. BEHAV. 2(5) 697–702, 1974. – Bilateral electrolytic lesions in the dorsal portion of the anterior striatum of adult male rats reliably increased spontaneous wheel running, and potentiated the stimulant effects of d,l-amphetamine on activity in both running wheels and stabilimeters. Comparable lesions in the ventral aspects of the striatum produced a decrease in spontaneous wheel running and did not modify the activating effects of amphetamine in either wheels or stabilimeters.

Amphetamine-locomotor effects Locomotor activity Striatal lesions

THE corpus striatum has been implicated in the modulation of sensorimotor functions [7] as well as electrophysiological and behavioral arousal [2]. It has been difficult to study the functional role of these striatal mechanisms because both facilitatory and inhibitory influences appear to be represented in this portion of the brain. Large striatal lesions produce hyperactivity [7,30], but a selective inactivation of dopaminergic components of the striatum as seen in Parkinson's disease [10] or after intracerebral injections of 6-hydroxydopamine [29] results in hypokinesia. Low frequency stimulation of the caudate nucleus of cats results in a general inhibition of behavior and synchrony of the cortical EEG, but high frequency stimulation of the same region induces behavioral as well as electrophysiological arousal [2].

There is some indication that the distribution of facilitatory and inhibitory mechanisms within the striatum may be sufficiently different to permit a selective activation or inactivation. Liles and Davis [17,18] have reported that cortical synchrony and motor inhibition are specifically produced by stimulation of ventral portions of the caudate. We [26] have similarly found that cholinoceptive components of the ventral but not dorsal striatum of rats exercise inhibitory influences on some complex behaviors.

The present report presents the results of experiments designed to further examine the possibility that facilitatory and inhibitory influences on arousal and motor functions may be distributed in anatomically distinct areas within the corpus striatum of rats.

EXPERIMENT 1

METHOD

Animals

Twenty four male albino rats of the Sprague-Dawley strain (Holtzman, Madison, Wis.) were used. All weighed 350–400 g at the time of surgery.

Apparatus

Thirteen Acme (Chicago, Ill.) activity wheels were used. These wheels were constructed of galvanized steel and measure 14 cm in width and 36 cm in diameter. A small 11 × 11 × 21 cm cage containing food (Teklad rat pellets) and

[1] Present address: Department of Psychology, Emory University, Atlanta, Georgia 30322.

[2] Please send reprint requests to Sebastian P. Grossman, Department of Psychology, University of Chicago, 5848 S. University Avenue, Chicago, Illinois 60637. This research was supported by United States Public Health Service Grant MH-10130 to S. P. Grossman.

water was attached to the side of each wheel. The wheels were housed in a quiet room separate from most laboratory activities. This room was on a 12 hr light-dark cycle, with light on from 10 a.m. to 10 p.m.

Procedure

Behavioral. Upon arrival in the laboratory, each animal was placed in an activity wheel and daily readings of the number of revolutions in the wheel were taken. After about 2–3 weeks, daily activity stabilized. Running activity in the light and dark portions of the light-dark cycle was then recorded separately for one week. Immediately after surgery (see below), the animals were returned to the running wheels and their activity in the light and dark phases of the light cycle was recorded for two additional weeks. Throughout the experiment, food and water were available ad lib.

Surgical. All animals received intraperitoneal (i.p.) injections of Nembutal (50 mg/kg) and atropine methyl nitrate (10 mg/kg) prior to stereotaxic surgery. Seven rats received bilateral dorsal striatal lesions, 8 received ventral striatal lesions, and 9 served as operated controls (scalp opened and burr holes placed in the skull, but the electrode was not lowered). The stereotaxic coordinates for these lesions were based on the results of previous experiments (e.g., [26]) which suggested functional distinctions between the dorsal and ventral striatum of the rat. The lesions were made by passing 2 mA of anodal direct current for 20 sec between the 0.5 mm uninsulated tip of a No. 3 stainless steel insect pin in the dorsal or ventral striatum and a saline pad on the tail. The stereotaxic coordinates, based on the Pellegrino and Cushman [27] atlas of the rat brain, were AP = 8.6; L = 2.7; H = 2.7 for the dorsal lesions and AP = 8.6; L = 2.7; H = 1.0 for the ventral lesions.

Evaluation of results. After completion of the behavioral tests the experimental animals were given i.p. injections of a lethal dose of Nembutal and were perfused intracardially with isotonic saline followed by 10% Formalin. Fifty-

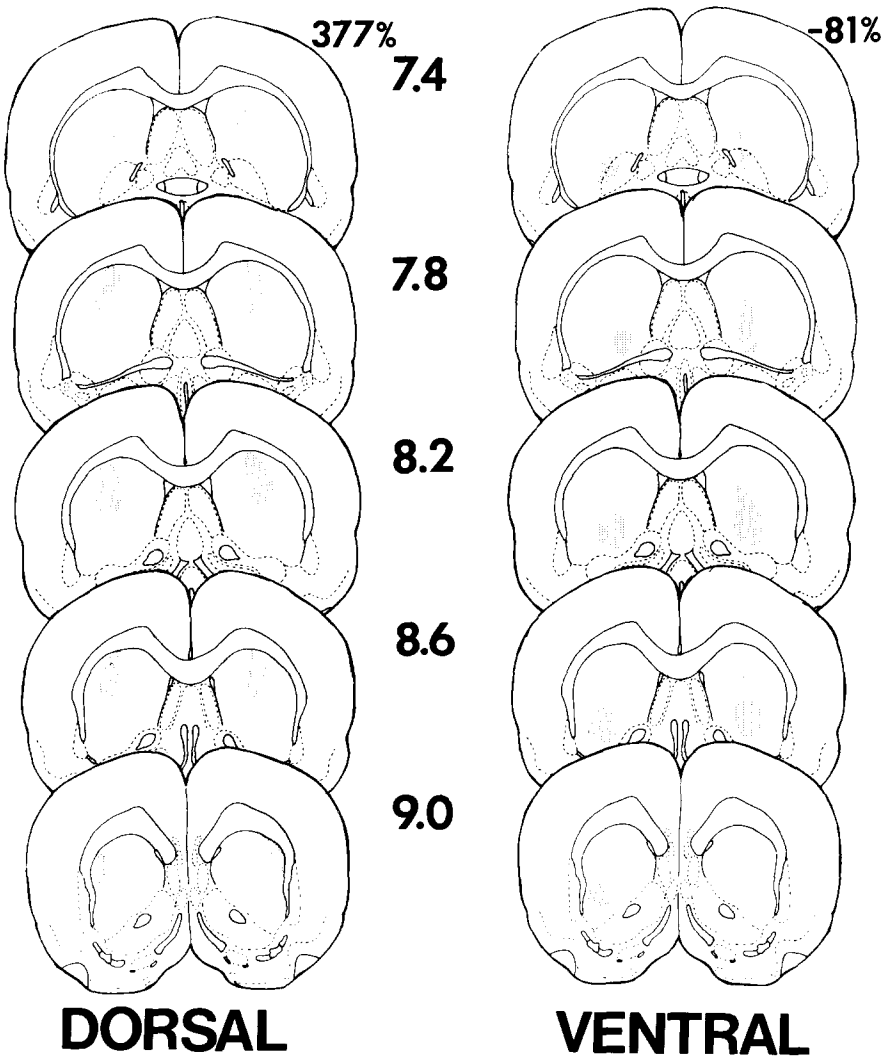

FIG. 1. Representative sections from 2 rats with lesions in the dorsal or ventral anterior striatum, based on the Pellegrino and Cushman [27] atlas of the rat brain. The percentages shown at the top of the illustration represent the change in running activity in the wheels seen after surgery.

micron frozen frontal sections were cut through the area of the lesions and stained with cresyl violet. The lesions were independently evaluated by two of us (D.N. and J.R.). The data from one animal with ventral damage were not included in the analysis because the lesions were asymmetric.

Changes in running activity were analyzed as percentages of pre-operative activity. The pre-operative baselines consisted of the averages of the 3 days immediately preceding surgery. The data from 2 rats (one control and one rat with ventral lesions) which ran more than 4,000 revolutions/day prior to surgery were not used. An overall analysis was performed, using the Kruskal-Wallis test [28]. Individual comparisons of groups were made with two-tailed Mann-Whitney U-tests [28].

RESULTS AND DISCUSSION

Representative lesions in the anterodorsal and anteroventral striatum are shown in Fig. 1. Anterodorsal lesions reliably ($p<0.01$) increased total daily activity (see Fig. 2). Ventral striatal lesions produced a moderate but reliable ($p<0.05$) decrease in activity. Both changes in activity were confined to the dark phase of the daily (12 hr on – 12 hr off) light cycle (see Table 1). Kirkby [14] has recently reported effects of large dorsal striatal lesions on open field activity which also appeared only during the dark.

It is interesting to note that the hyperactivity did not appear immediately after surgery, but developed gradually during the first week after surgery. An examination of data from individual animals indicated that the gradual increase was not an artifact of averaging. Additional activity readings taken after the amphetamine tests reported below (Experiment 2) showed that four weeks after surgery, rats with lesions in the dorsal striatum were still running approximately as much ($\bar{X}$ = 2949) as they were two weeks after surgery ($\bar{X}$ = 2545). These observations indicate that the hyperactivity develops slowly after the dorsal lesions, reaches a maximum in approximately 10 days, and remains at that level for at least another 2 weeks.

It is possible that the gradual development of hyperactivity following lesions in the dorsal striatum may be related to a depletion of dopamine or other transmitter which has been shown to have a similar time course after various lesions [9]. However, other explanations cannot be ruled out at this time. It is, for instance, plausible that the dorsal lesions may result in incidental damage to whatever mechanisms are responsible for the persisting hypoactivity seen after lesions in the ventral striatum. This would account for the hypoactivity seen in rats with dorsal lesions during the first few days after surgery, and might explain the gradual development of hyperactivity if one assumes that the facilitatory effects of the dorsal lesions cannot

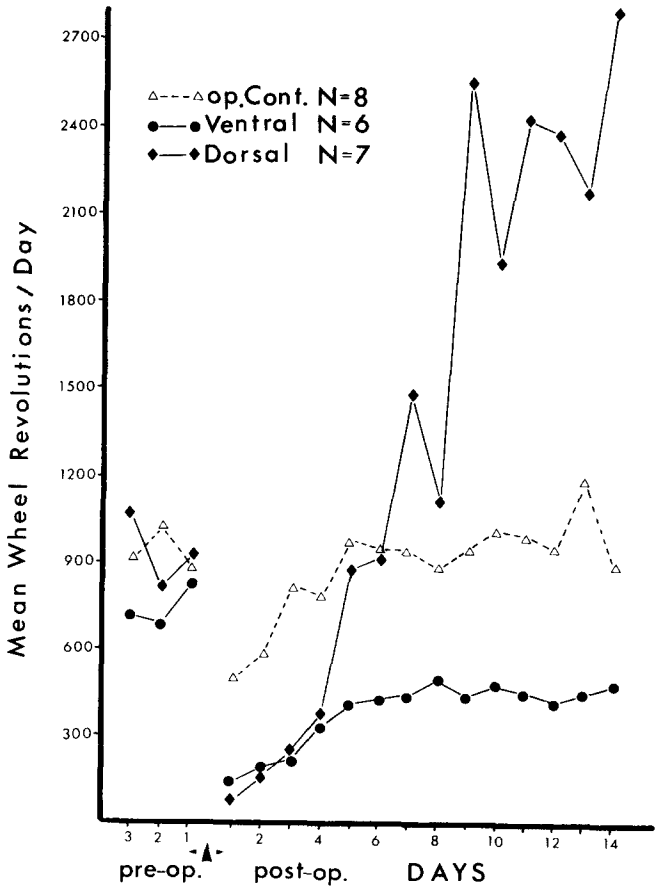

FIG. 2. Mean number of revolutions of a running wheel per day before and after lesions in the dorsal or ventral striatum.

TABLE 1

AVERAGE (±SEM) NUMBER OF REVOLUTIONS OF ACTIVITY WHEELS ON 3 DAYS PRIOR TO SURGERY (PRE) AND ON DAYS 12–14 AFTER SURGERY (POST) IN THE LIGHT AND DARK PORTIONS OF A 12 HR LIGHT–DARK CYCLE

		Light		Dark	
Group	n	Pre	Post	Pre	Post
Op. Cont.	8	112 ± 32	120 ± 42	835 ± 301	881 ± 419
Ventral lesions	6	143 ± 46	134 ± 36	604 ± 203	323 ± 70*
Dorsal lesions	7	155 ± 47	334 ± 200	779 ± 196	2211 ± 796†

*$p<0.05$, †$p<0.01$, based on an analysis of percentages of pre-op activity

become fully apparent until a partial recovery of the functions of the ventral striatum has occurred.

EXPERIMENT 2

Damage to several brain structures which seem to exert inhibitory influences on locomotor activity has been shown to potentiate the arousing effect of CNS stimulants. The activating effects of amphetamine, for instance, are potentiated by lesions in the frontal cortex [12,20], septum [4], hippocampus [3], and the region of the raphé nuclei [25] of the rat. The following experiments were conducted to examine the possibility that dorsal but not ventral striatal lesions may produce similar effects.

Because several investigators have demonstrated that drugs or CNS lesions often have different effects on locomotor activity in wheels and stabilimeters (e.g., [19]), both types of apparatus were used.

METHOD

Animals

Eight operated controls, 6 rats with lesions in the ventral striatum and 7 rats with lesions in the dorsal striatum were tested in the running wheels. Six of the operated controls and 5 rats from each of the experimental groups were also tested in the stabilimeters. All animals had previously served in Experiment 1.

Apparatus

The activity wheels described above (Experiment 1) were used. Activity was also measured in four 37.5 × 17.5 × 20 cm stabilimeters constructed of Plexiglas. Movement of the animal across a central fulcrum of the grid floors caused it to tilt slightly and depress a microswitch which activated a counter. The stabilimeters were housed in a dark, sound-attenuating chamber.

Procedure

All animals were housed in running wheels with food and water available in an adjacent compartment for 2–3 weeks prior to surgery and for 2 weeks afterwards. On the 15th day after surgery, each animal received an i.p. injection of 1.0 ml/kg of isotonic saline. Intraperitoneal injections of 2.0, 1.0, and 3.0 mg/kg of d,l-amphetamine sulfate in a volume of 1 ml/kg were given 48, 96, and 120 hr respectively after the first saline injection. A second saline injection was given 48 hr after the last drug test. The drug effects were compared to data obtained during the second saline control test.

Following completion of the wheel running experiment described above, all animals were housed individually in a continuously illuminated colony. Food and water were available ad lib. Every fourth day, each animal was placed into a stabilimeter apparatus and its activity was recorded every 1/2 hr for 1 1/2 hr. Saline or amphetamine were then injected i.p. in the doses and volumes used in the preceding experiment and activity was recorded every 1/2 hr for 4 additional hr. The sequence of saline and drug tests was identical to that described for the wheel experiment.

Evaluation of results. The group effects of the three doses of amphetamine on activity in both wheels and stabilimeters were subjected to an overall analysis of variance for repeated measures [31]. Individual groups were then compared using the method of least squares ([31], pp. 377–378).

Only the data from rats which showed a clear change in baseline activity as a result of striatal lesions were included in these analyses. The data from one rat with dorsal lesions were excluded from the analysis of both experiments because it failed to show evidence of hyperactivity in any of our tests. The data from a second rat with dorsal lesions were excluded only from the analysis of the stabilimeter experiment because its initially increased activity returned to preoperative levels before that test was begun. These observations suggest that lesions in the dorsal striatum may result in persistent effects on locomotor activity only when certain critical elements of the region are destroyed. Attempts to identify these structures on the basis of our anatomical data were not successful.

RESULTS

The stimulant effects of 1.0, 2.0 and 3.0 mg/kg of amphetamine on running activity in the wheel apparatus were reliably ($p<0.01$) larger in rats with lesions in the dorsal striatum than in operated controls or in rats with lesions in the ventral striatum. There were no reliable differences ($p<0.25$) between the reactions of the control group and the group with lesions in the ventral striatum (see Fig. 3). The saline baseline for these drug tests was not reliably different in these tests. This is in accordance with the results of Experiment 1 which demonstrated that lesions in the dorsal and ventral striatum affect activity only during the dark phase of the light-dark cycle.

An analysis of the data from the stabilimeter experiment demonstrated a similar pattern of effects (see Fig. 4). Amphetamine produced larger effects in rats with lesions in the dorsal striatum than in controls or in rats with ventral striatal damage ($p<0.01$) and there were no reliable differences between the latter two groups. The baselines of the three groups were comparable ($p>0.25$), indicating that stabilimeter activity is also not affected by either striatal lesion even though the tests were conducted in the dark.

These results suggest that lesions in the anterodorsal striatum which increased spontaneous wheel-running in the dark also increased the locomotor effects of amphetamine as measured in two types of activity apparatus. In the wheels, the peak running activity under amphetamine was significantly correlated with spontaneous running measured 2 weeks after surgery (rho = 0.88, $p<0.05$). The correlation between peak drug-induced activity in the stabilimeters and the level of spontaneous wheel activity immediately preceding the stabilimeter tests (4 weeks after surgery) was weaker (rho = 0.75, $0.05<p<0.10$).

GENERAL DISCUSSION

The results of the present experiments, viewed in conjunction with those of an earlier investigation [24], indicate that the striatum may exert complex influences on locomotor activity in the rat which become apparent only under certain circumstances. Our results suggest that the dorsal portions of the striatum may be a source of inhibitory influences and that the stimulant effects of amphetamine on locomotor activity may be related, at least in part, to the drug's action on mechanisms which are normal-

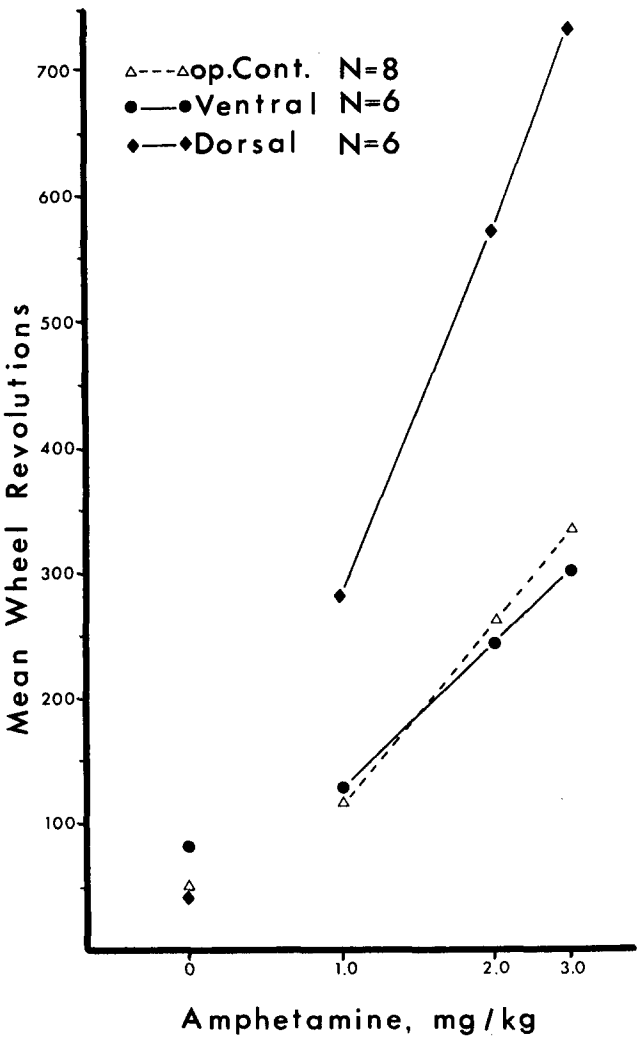

FIG. 3. Mean number of revolutions of a running wheel during 4 hr tests after the i.p. administration of various doses of d,l-amphetamine.

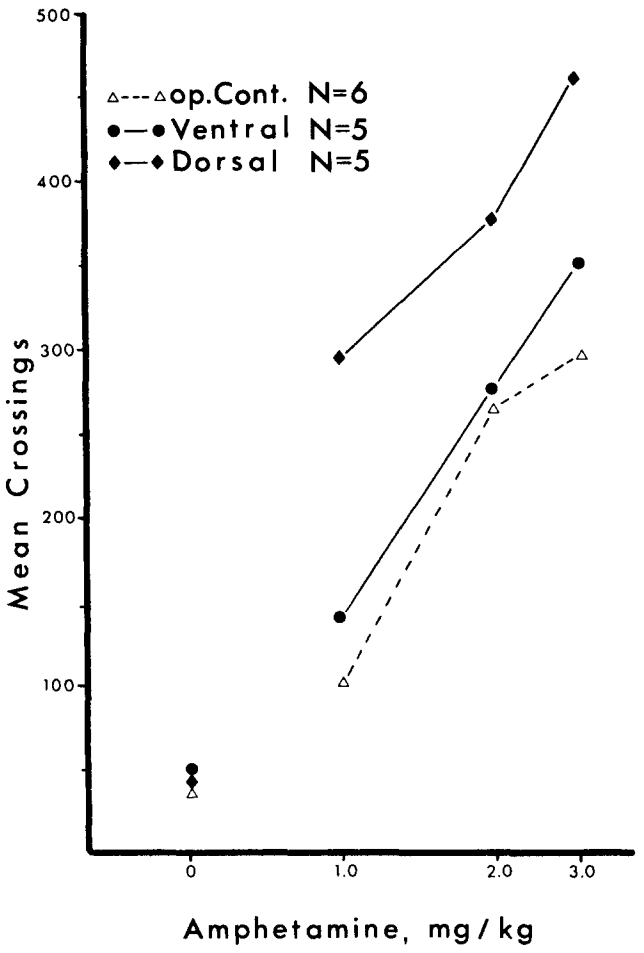

FIG. 4. Mean activity in stabilimeters during 4 hr tests after the i.p. administration of various doses of d,l-amphetamine.

ly inhibited by components of the dorsal striatum. Under some test conditions, the ventral striatum appears to exert excitatory influences on locomotor activity. The locomotor effects of amphetamine appear to be independent of these ventral striatal influences.

Lesions in the dorsal striatum increased locomotor activity in our experiments but the effects were small unless baseline activity was relatively high. Thus, wheel running was markedly increased in the dark but not in the light, only small effects were seen in an open field, and there were none in stabilimeters unless the animals were tested under amphetamine. Other investigators (e.g., [14]) have reported facilitatory effects of large striatal lesions on activity under conditions such as food deprivation, which produce relatively high baseline activity.

The stimulant effects of amphetamine on locomotor activity were reliably potentiated in wheels (even in the light phase of the cycle) and in stabilimeters. Facilitatory effects were also seen in the open field but they were small and did not satisfy customary criteria of statistical reliability. A significant potentiation of the amphetamine effect on locomotion was observed even in a test paradigm (spontaneous locomotion in a shuttle box during the intertrial interval) which showed an initial depression of activity after the lesion (see [24]).

A similar pattern of effects – increased spontaneous activity and a potentiation of the locomotor effects of amphetamine – has been seen after damage to the dorsal frontal cortex of rats [12]. In conjunction with anatomical observations which indicate that the dorsolateral frontal cortex projects topographically to the dorsal aspects of the striatum in the rat [16] as well as the monkey [13] this suggests that our dorsal lesions may interfere with aspects of a fronto-striatal projection system.

Lesions in the ventral striatum produced persisting inhibitory effects on wheel running in the dark but no effects at all on activity in the open field or in stabilimeters. Amphetamine produced effects on activity in wheels, the open field, and in stabilimeters which were indistinguishable from those seen in controls. Ventral striatal lesions inhibited intertrial activity in the avoidance apparatus but this effect is difficult to interpret since they also markedly impaired the performance of avoidance behaviors in the same apparatus. Neither the depression of intertrial activity

nor the concurrent inhibition of avoidance responding were reversed by amphetamine (see [24]).

The consistently normal response to amphetamine of rats with lesions in the ventral striatum is consistent with earlier reports of the effects of striatal lesions [22] or of 6-hydroxydopamine injections into the substantia nigra which deplete striatal dopamine [5]. There is, however, some evidence to suggest that an interference with the dopaminergic components of the ventral striatum might be responsible for the decreased spontaneous activity which is seen under some circumstances. Neill [23], for instance, has observed an increase in activity after direct applications of dopamine to the ventral striatum, and Ungerstedt [29] has reported that injections of 6-hydroxydopamine into the nigrostriatal bundle depleted striatal dopamine and produced marked hypokinesia. The conclusion is also congruent with the clinical observation that the "poverty of moment" typical of Parkinson's disease has been associated with a loss of striatal dopamine [10].

It may be important, at this point, to emphasize that lesions in the dorsal striatum do not potentiate all effects of amphetamine, and that lesions in the ventral striatum do, in fact, modify some of the effects of this drug (e.g., we [24] have earlier reported that the stereotypy which is seen after very high doses of amphetamine is not reliably affected by dorsal lesions but is reliably affected by ventral lesions of similar size).

REFERENCES

1. Buchwald, N. A., E. J. Wyers, C. W. Lauprecht and G. Heuser. The "caudate-spindle" IV. A behavioral index of caudate-induced inhibition. *Electroenceph. clin. Neurophysiol.* **13:** 531–537, 1961.
2. Buchwald, N. A., E. J. Wyers, T. Okuma and G. Heuser. The "caudate-spindle" I. Electrophysiological properties. *Electroenceph. clin. Neurophysiol.* **13:** 509–518, 1961.
3. Campbell, B. A., P. Ballantine and G. Lynch. Hippocampal control of behavioral arousal: Duration of lesion effects and possible interactions with recovery after frontal cortical damage. *Expl Neurol.* **33:** 159–170, 1971.
4. Carey, R. J. and A. P. Salim. Changes in d-amphetamine reactivity resulting from septal forebrain injury. *Physiol. Behav.* **5:** 133–136, 1970.
5. Creese, I. and S. D. Iversen. Amphetamine response in rat after dopamine neurone destruction. *Nature New Biol.* **238:** 247–248, 1972.
6. D'Anna, L. and G. Krauthamer. Distribution dans la capsule interne et le noyau caude des zones qui inhibent les activités corticales non spécifiques. *J. Physiol. (Paris)* **56:** 330–331, 1964.
7. Denny-Brown, D. *The Basal Ganglia.* London: Oxford University Press, 1962.
8. Grossman, S. P. Behavioral effects of chemical stimulation of the ventral amygdala. *J. comp. physiol. Psychol.* **57:** 29–36, 1964.
9. Heller, A. and R. Y. Moore. Control of brain serotonin and norepinephrine by specific neural systems. In: *Advances in Pharmacology, Vol. 6,* edited by S. Garattini and P. A. Shore. New York: Academic Press, 1968.
10. Hornykiewicz, O. Dopamine (3-hydroxytyramine) and brain function. *Pharmac. Rev.* **18:** 925–964, 1966.
11. Isaac, W. and J. L. DeVito. Effect of sensory stimulation on the activity of normal and prefrontal-lobectomized monkeys. *J. comp. physiol. Psychol.* **51:** 172–174, 1958.
12. Iversen, S. D. The effect of surgical lesions to frontal cortex and substantia nigra on amphetamine responses in rats. *Brain Res.* **31:** 293–311, 1971.
13. Johnson, T. N., H. E. Rosvold and M. Mishkin. Projections from behaviorally-defined sectors of the prefrontal cortex to the basal ganglia, septum and diencephalon of the monkey. *Expl Neurol.* **21:** 20–34, 1968.
14. Kirkby, R. J. Caudate nucleus and arousal in the rat. *J. comp. physiol. Psychol.* **85:** 82–96, 1973.
15. Kostowski, W., E. Giacalone, S. Garattini and L. Valzelli. Studies on behavioural and biochemical changes in rats after lesion of midbrain raphé. *Eur. J. Pharmac.* **4:** 371–376, 1968.
16. Leonard, C. M. The prefrontal cortex of the rat. I. Cortical projections of the mediodorsal nucleus. II. Efferent connections. *Brain Res.* **12:** 321–343, 1969.
17. Liles, S. L. and G. D. Davis. Interrelation of caudate nucleus and thalamus in alteration of cortically induced movement. *J. Neurophysiol.* **32:** 564–573, 1969.
18. Liles, S. L. and G. D. Davis. Electrocortical effects of caudate stimulations which alter cortically induced movement. *J. Neurophysiol.* **32:** 574–582, 1969.
19. Lynch, G. S. Separable forebrain systems controlling different manifestations of spontaneous activity. *J. comp. physiol. Psychol.* **70:** 48–59, 1970.
20. Lynch, G. S., P. Ballantine and B. A. Campbell. Potentiation of behavioral arousal after cortical damage and subsequent recovery. *Expl Neurol.* **23:** 195–206, 1969.
21. McKenzie, J. S., D. M. Gilbert and D. K. Rogers. Hippocampal and neostriatal inhibition of extralemniscal thalamic unitary responses in the cat. *Brain Res.* **27:** 382–385, 1971.
22. Naylor, R. J. and J. E. Olley. Modification of the behavioural changes induced by amphetamine in the rat by lesions in the caudate nucleus, the caudate-putamen, and globus pallidus. *Neuropharmacology* **11:** 91–99, 1972.
23. Neill, D. B. Striatal chemical mechanisms and behavioral inhibition. Unpublished doctoral dissertation, University of Chicago, 1972.
24. Neill, D. B., W. O. Boggan and S. P. Grossman. Behavioral effects of amphetamine in rats with lesions in the corpus striatum. *J. comp. physiol. Psychol.* **86:** 1019–1030, 1974.
25. Neill, D. B., L. D. Grant and S. P. Grossman. Selective potentiation of locomotor effects of amphetamine by midbrain raphé lesions. *Physiol. Behav.* **9:** 655–657, 1972.
26. Neill, D. B. and S. P. Grossman. Behavioral effects of lesions or cholinergic blockade of the dorsal and ventral caudate of rats. *J. comp. physiol. Psychol.* **71:** 311–317, 1970.
27. Pellegrino, L. J. and A. J. Cushman. *A Stereotaxic Atlas of the Rat Brain.* New York: Appleton-Century-Crofts, 1967.
28. Siegel, S. *Nonparametric Statistics for the Behavioral Sciences.* New York: McGraw-Hill, 1956.
29. Ungerstedt, U. Adipsia and aphagia after 6-hydroxydopamine induced degeneration of the nigro-striatal dopamine system. *Acta physiol. scand. Suppl.* **367:** 95–122, 1971.
30. Whittier, J. R. and H. Orr. Hyperkinesis and other physiological effects of caudate deficit in the adult albino rat. *Neurology* **12:** 529–534, 1962.
31. Winer, B. J. *Statistical Principles in Experimental Design.* New York: McGraw-Hill, 1962.