Pharmacology Biochemistry & Behavior, Vol. 12, pp. 603–608. Printed in the U.S.A.

Effects of Lesions of the Ventral Medial Tegmentum on Locomotor Activity, Biogenic Amines and Response to Amphetamine in Rats[1]

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Received 15 September 1979

SESSIONS, G. R., J. L. MEYERHOFF, G. J. KANT AND G. F. KOOB. *Effects of lesions of the ventral medial tegmentum on locomotor activity, biogenic amines and response to amphetamine in rats.* PHARMAC. BIOCHEM. BEHAV. 12(4) 603–608, 1980.—Rats subjected to electrolytic lesions of the ventral medial tegmentum (VMT) showed long-lasting increased locomotor activity in the open field compared to sham-operated controls. In addition to severe depletion of mesolimbic dopamine, the lesions also caused significant depletions of striatal dopamine, mesolimbic and striatal norepinephrine and striatal and hippocampal serotonin. Administration of *d*-amphetamine sulfate produced similar dose-response functions for locomotor activity in both VMT-lesioned and sham-operated rats despite the extensive depletion of dopamine in the VMT-lesioned rats. These results suggest that the mesolimbic dopamine pathway is not the sole substrate for amphetamine-stimulated locomotor activity. Electrolytic lesions of the VMT interrupt several neurotransmitter pathways which may produce complex and antagonistic effects on behavior.

Ventral medial tegmentum A10 Dopamine Norepinephrine Serotonin Activity Amphetamine Lesions

SEVERAL neuronal systems containing dopamine have been described using histofluorescence histochemistry and biochemical mapping [1, 2, 9, 12, 21, 37]. The nigrostriatal pathway projects rostrally from cell bodies in the zona compacta of the substantia nigra to the corpus striatum. Another group of dopaminergic cells, located medial to the zona compacta and dorsolateral to the interpenduncular nucleus in the ventral medial tegmentum (VMT), projects to the nucleus accumbens and olfactory tubercle. This pathway has been termed the mesolimbic dopamine system.

Much work supports the hypothesis that the nigrostriatal dopamine system is the dopamine pathway involved in stereotyped behavior induced by high doses of amphetamine. Electrolytic and 6-hydroxydopamine lesions of the corpus striatum have been shown to reduce or abolish stereotyped behavior induced by amphetamine [6, 10, 27]. 6-Hydroxydopamine lesions of the substantia nigra also abolish the stereotyped behavior induced by amphetamine [7]. Further, injection of dopamine into the corpus striatum induces stereotyped behavior [8, 11, 36].

The role of the mesolimbic dopamine system has not been as extensively explored, but evidence suggests that the mesolimbic dopamine system is functionally different from the nigrostriatal system. Injections of dopamine into the nucleus accumbens produce a strong and long-lasting enhancement of locomotor activity [29]. Further, 6-hydroxydopamine lesions of the nucleus accumbens and olfactory tubercle abolish the locomotor response to amphetamine, but fail to alter the stereotyped behavior induced by high doses of amphetamine [20]. These reports which suggest that the mesolimbic dopamine pathway may be the neuronal substrate mediating amphetamine-induced hyperactivity are hard to reconcile with observations that electrolytic and 6-hydroxydopamine lesions of the region of the ventral medial tegmentum itself produce a long-lasting hyperactivity syndrome [13, 22, 34, 35].

In a preliminary study we examined the amphetamine locomotor response of rats with the electrolytic lesions of the VMT in an attempt to determine if the integrity of the mesolimbic dopamine pathway is essential for this response.

[1]In conducting the research described in this report, the investigators adhered to the 'Guide for Laboratory Animal Facilities and Care,' as promulgated by the Committee of the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Sciences, National Research Council. This material has been reviewed by the Walter Reed Army Institute of Research, and there is no objection to its presentation and/or publication. The opinions or assertations contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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The results suggested that the VMT-lesioned rats were not only responsive to amphetamine, but appeared to show greater hyperactivity than controls [31]. The present work examined this effect more closely by observing the locomotor response of VMT- and sham-lesioned rats to *d*-amphetamine in doses ranging from 0.25 to 4.0 mg/kg.

Since fibers from other amine systems pass through the region of the VMT, we also determined the extent to which electrolytic VMT lesions interrupt other dopaminergic, noradrenergic or serotonergic systems.

METHOD

Animals

The subjects were 23 Wistar-derived Walter Reed strain male albino rats weighing 300 grams at the time of surgery. The animals were housed individually in standard rat cages with grid floors in an air conditioned animal room which was maintained at approximately 23°C under a 12 hr light/dark cycle with light onset at 0600 hours. Purina rat chow and water were freely available throughout the experiment, except during activity test sessions.

Surgical Procedures

The rats were anesthetized with sodium pentobarbital (50 mg/kg IP) and immobilized in a stereotaxic instrument. Stainless steel electrodes, 0.25 mm in diameter and insulated to within 0.5 mm of the rounded tip (Kopf, Inc.), were lowered bilaterally through burrholes in the skulls to placements aimed at the ventral medial tegmentum. Coordinates with the calvarium level between bregma and lambda were 3.0 mm rostral to ear bar zero, lateral 0.6 mm from midline and ventral 8.5 mm from the surface of the skull. Lesions were produced in 13 animals by passage of 1.0 mA DC current to a rectal cathode for 10 sec. Surgical sham-operated controls consisted of four animals with burrholes drilled without electrode penetrations and six animals with electrode penetration to the border of the VMT but without lesions. Two of the animals in the lesion group died within 24 hours of surgery and one died before the end of the behavioral testing, leaving 10 animals each in the lesion and control groups.

Drugs

Dextro-amphetamine sulfate was dissolved in 0.9% saline immediately prior to intraperitoneal injection. Doses are expressed as the sulfate.

Behavioral Testing

The first part of the study was designed to measure the initial locomotor activity of the animals in the open field and to habituate them to the testing apparatus before drug injections. Due to the debilitating effects of the lesion a recovery period of 25–26 days was allowed before behavioral testing was begun. Then the animals received 30-min activity tests once a day for 5 consecutive days in Lehigh Valley open-field photocell cages (BRS Foringer, Beltsville, MD). These open-field activity cages consisted of circular arenas 61 cm in diameter with grid floors and metal walls 41.3 cm high. Two banks of 3 photocells each aligned perpendicularly to each other detected movements along the grid floor. Electronic recording equipment connected to the photocells recorded the number of beam breaks in each cage during 5-min intervals. The cages were lighted only by the dim light beams of the photocell array. Masking noise was introduced into each cage through speakers mounted in the cage lids. Activity testing was conducted between 1300 and 1600 hours.

The second part of the experiment examined the effects of *d*-amphetamine upon locomotor activity. Beginning 3 days after the last habituation test the animals again received 30-min activity tests once a day, and every third day they were injected with either 0.0, 0.25, 0.50, 1.0, 2.0, 3.0, or 4.0 mg/kg of *d*-amphetamine sulfate, 15 minutes before the beginning of the activity testing. The day prior to each drug day the animals were injected with saline in equivalent volume before testing. The day following each drug day no injections were given prior to testing. Five no-drug days separated the higher doses of 3.0 and 4.0 mg/kg from the other doses. Drug doses were administered in a non-systematic order.

Biochemical Methods

Animals were sacrificed and their brains were regionally analyzed for norepinephrine, dopamine and serotonin content. The animals were sacrificed by decapitation, their brains quickly removed, and the corpus striatum, nucleus accumbens and olfactory tubercle were dissected as described previously [21]. The hippocampus was removed by blunt dissection. Tissue from the nucleus accumbens and olfactory tubercle were pooled as one region and together with the corpus striatum were assayed for dopamine and norepinephrine by the radioenzymatic method of Coyle and Henry [4]. Striatum and also hippocampus were analyzed for serotonin by a fluorometric method [32,33]. All measures were corrected for recovery.

Histology

The intact midbrain and brainstem portion of the brain not used for biochemical analyses was fixed in 10% Formalin. Serial sections 52 μm thick were cut on a freezing microtome and every other section through the lesion was stained with cresylectviolet.

RESULTS

Lesions

As defined for this study, the ventral medial tegmentum lies medial to the substantia nigra, surrounding the dorsolateral border of the interpenduncular nucleus. The lesions were approximately 1 mm in diameter bilaterally and extended from just anterior to the rostral pons to just caudal to the mammillary bodies. The ventral medial tegmentum sustained extensive damage in all animals (see representative section in Fig. 1). The interpeduncular nucleus and the most medial aspects of the medial lemniscus often sustained moderate damage.

Post-operative Recovery

Seven out of 10 animals in the lesion group failed to eat rat pellets following surgery and were maintained on a palatable liquid diet (Sustagen diet, Mead Johnson and Co.) until they began eating solid food. The lesioned rats lost 17% of their preoperative body weight (mean preoperative value: 296 g) in the first four days following the lesion and the control animals lost 10% (mean preoperative value: 299 g) during this period. The lesioned rats showed normal weight gains following this initial period and had recovered to their preoperative body weight by Day 18 (Day 12 for the control

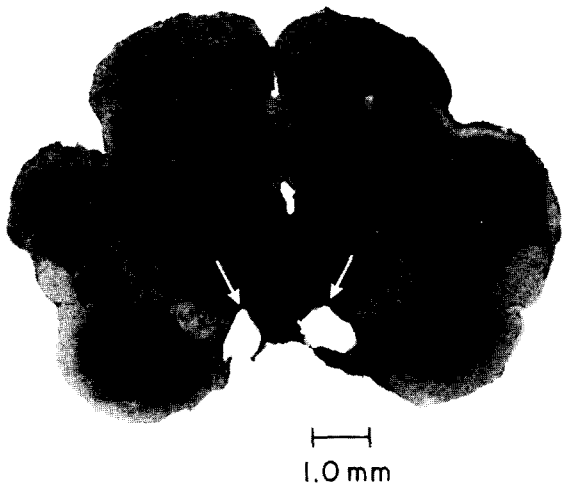

FIG. 1. Photomicrograph of a cresylectviolet-stained section through the midbrain of a representative VMT-lesioned animal at the level of the superior colliculus. Amine depletion levels of this animal, relative to average level of sham-operated controls, were nucleus accumbens-olfactory tubercle: dopamine 85%, norepinephrine 44%; striatum: dopamine 58%, norepinephrine 22%, serotonin, 37%; hippocampus: serotonin 37%.

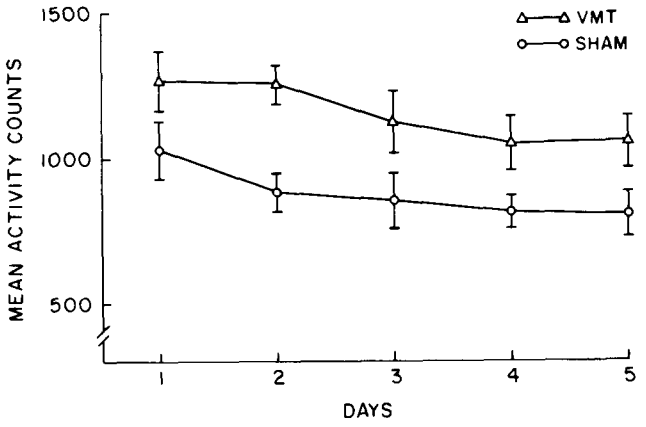

FIG. 2. Mean activity counts for first five 30-minute activity tests for VMT-lesioned and sham-operated rats. Day 1 of testing is the 26th postoperative day. Values represent the mean ± SEM with N=10 in each group.

rats). Although gaining weight at normal rates, the lesioned rats remained at 88 to 92% of the average sham weight for the duration of the experiment.

Locomotor Activity

The locomotor activity of the lesion rats in the open field was significantly greater than that of sham-operated controls during the five habituation trials (postoperative Days 26–31) as shown in Fig. 2. A repeated measures analysis of variance (ANOVA) revealed a significant group effect, $F(1,18)=8.68$, $p<0.01$, and a significant reduction in activity across days, $F(4,72)=4.90$, $p<0.01$, with no significant interaction. In both groups the highest activity levels were observed during the first 5 min, followed by a gradual decline in activity over the subsequent 5-min periods as shown in Fig. 3.

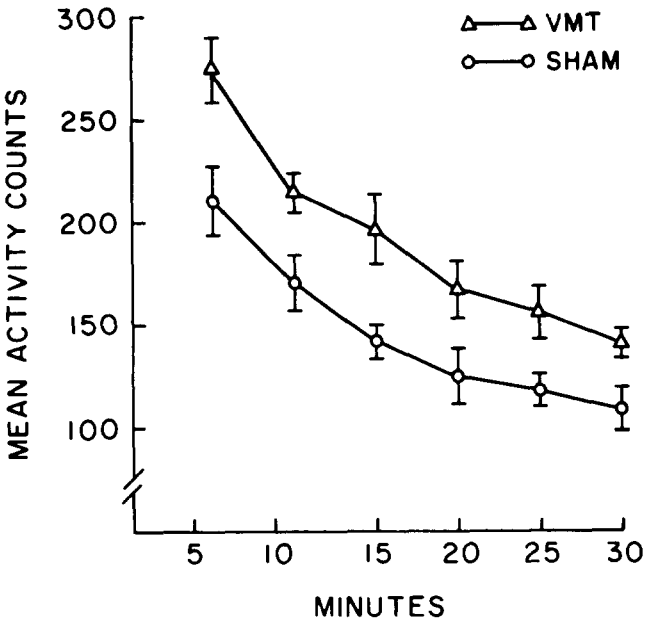

FIG. 3. mean activity counts over 5 minute intervals for first five activity tests for VMT-lesioned and sham-operated rats. Values represent the mean ± SEM with N=10 in each group.

The hyperactivity observed during this initial habituation period lasted for the duration of the experiment. The ANOVA performed on activity scores for both groups of animals on nine saline injection days (between Days 31 and 57) again revealed a significant group effect, $F(1,18)=6.86$, $p<0.05$, and a significant days effect, $F(8,144)=2.30$, $p<0.05$, but no groups by days interaction.

Both the VMT and sham-lesioned groups showed inverted U-shaped dose response curves after *d*-amphetamine administration as shown in Fig. 4. Although the VMT animals exhibited higher baseline activity, the amphetamine-stimulated activity across doses was not significantly different from that of the sham-operated controls. Analyses of variance revealed no significant differences between groups, and no significant group by dose interactions regardless of whether the analyses were conducted on raw activity counts or on data normalized as percent activity increase over baseline levels. Further analysis of the doses at which the peak activity response of individual animals occurred showed no significant differences between the VMT- and sham-lesioned groups (Mann-Whitney U test, $U=48$, $p>0.50$).

Biochemical Results

The VMT lesions produced significant reductions in dopamine, norepinephrine and serotonin in all of the regions assayed as can be seen in Table 1. The lesions produced an average of 80 and 44% depletion of dopamine in the nucleus accumbens/olfactory tubercle and corpus striatum respectively, expressed as percent reduction from the average level for sham-operated animals. Norepinephrine was also significantly decreased in these two regions by approximately 35% as can be seen in Table 1. Serotonin levels were significantly decreased in both the striatum and hippocampus by 58 and 46%, respectively.

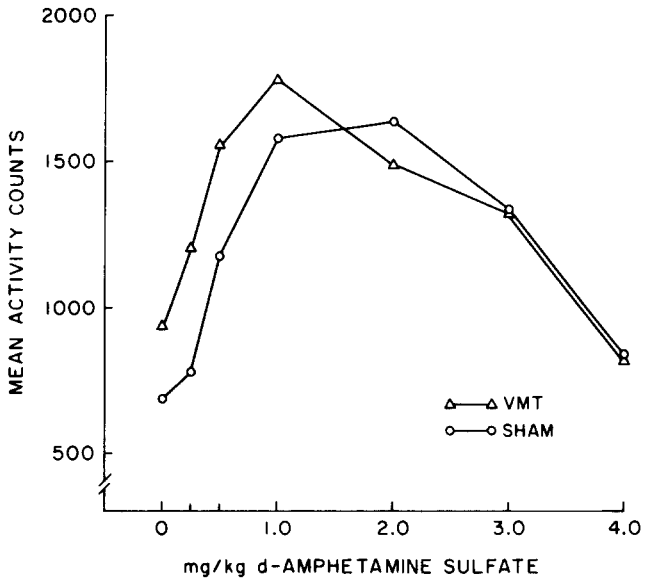

FIG. 4. Mean activity counts during 30-min activity tests beginning 15 min after administration of *d*-amphetamine sulfate for VMT-lesioned and sham-operated rats. The 0.0 dose represents the mean activity on saline injection days prior to drug injection days. Drug testing was conducted between the 35th and 57th postoperative days.

Correlational analyses were performed relating regional depletions of monoamines to the mean level of activity over the first five non-drug activity sessions. The only statistically significant relationship was between striatal dopamine depletion and mean activity level (Spearman Rho: -0.64, $n=10$, $p<0.05$, two-tailed). Correlations between the remaining regional depletions and activity ranged between 0.34 and -0.33 ($p>0.05$).

DISCUSSION

These results confirm and extend the observation that lesions in the region of the ventral medial tegmentum produce a sustained hyperactivity in the open field [13, 22, 31, 34, 35]. In addition the present work shows that VMT-lesioned rats respond to a range of doses of *d*-amphetamine in a manner similar to controls despite extensive damage to the mesolimbic dopamine pathway. Our preliminary observations of a tendency toward greater amphetamine sensitivity in VMT-lesioned animals was not confirmed [31]. Amphetamine injections produced a similar increase in activity over baseline levels in both VMT-lesioned and control animals. In addition, individual animals' dose response functions showed that the dose at which the lesioned animals showed a peak locomotor response was not reliably different from non-lesioned animals.

Other investigations [23] have reported that VMT-lesioned rats respond to amphetamine faster than controls in the first ten min following drug administration, yet respond less in the second hour following the drug. Our results showed no evidence of differential response to the drug between groups during the time periods studied, i.e., between 15 and 45 min following drug administration.

In view of other work on the mesolimbic dopamine system, it is difficult to account for either the VMT hyperactivity or the lack of alteration of locomotor response to amphetamine in terms of dopamine depletion in the accumbens/tubercle area alone. Injection of dopamine into the region of the nucleus accumbens elicits a sustained hyperactivity [29], and selective destruction of the dopamine terminals in this region with 6-hydroxydopamine abolishes the hyperactive response to amphetamine [20]. In addition, recent evidence suggests that rats with this 6-hydroxydopamine lesion are hypoactive during habituation [17].

Clearly, alterations in amphetamine stimulated locomotor activity can be achieved with more extensive manipulations of forebrain dopamine systems. Extensive dopamine depletions induced by intranigral injections of 6-hydroxydopamine have been shown to attenuate, but not abolish, the locomotor response to amphetamine [5,30].

It is possible that the damage inflicted to other neurotransmitter systems was primarily responsible for the behavior observed in this study. The biochemical findings reported here document that electrolytic lesions of the VMT produce depletions of norepinephrine as well as dopamine in both the nigrostriatal and mesolimbic terminal areas and depletions of serotonin in the striatum and hippocampus. Although acetylcholine levels were not measured in this study, lesions in the area of the VMT might also be expected to interrupt the habenulo-interpeduncular pathway, which has been shown to be cholinergic [14,24]. In addition, the area of the ventral medial tegmentum is densely crossed by fibers from the serotonergic systems ascending to the forebrain [26,37], and depletions of serotonin would be expected from lesions in this area. Lesions to the median raphe have been shown to produce hyperactivity [18,28] thought to be localized to the serotonin innervation of the hippocampus [19]. Other investigators have observed enhanced amphetamine locomotor responses in rats with raphe lesions [28], or in rats fed a tryptophan-free diet [16], and recently it has been shown that rats with lesions in the median raphe show an enhanced locomotor response to dopamine injected into the nucleus accumbens [3]. However, depletion of forebrain serotonin

TABLE 1

REGIONAL FOREBRAIN LEVELS OF DOPAMINE, NOREPINEPHRINE AND SEROTONIN IN VMT-LESIONED AND SHAM-OPERATED RATS, VALUES EXPRESSED AS μg AMINE/g WET WEIGHT

	Dopamine	Norepinephrine	Serotonin
Nucleus accumbens/ Olfactory tubercle			
Sham	11.27 ± 0.54	0.89 ± 0.09	—
VMT	2.19 ± 0.39*	0.55 ± 0.08*	—
Corpus striatum			
Sham	13.54 ± 0.47	0.35 ± 0.03	0.41 ± 0.03
VMT	7.47 ± 0.63*	0.23 ± 0.03*	0.17 ± 0.02*
Hippocampus			
Sham	—	—	0.35 ± 0.03
VMT	—	—	0.19 ± 0.04*

Values represent the mean ± SEM of 10 determinations except for the serotonin values where one sample was lost during the assay in both the lesion and sham groups. Comparisons between groups were made by Student's *t*-test.

*Differs from sham group $p<0.05$.

by intracerebral injection of 5,7 dihydroxytryptamine fails to produce this hyperactivity syndrome [15,25]. Further, the present study supports other work [35] which showed that forebrain serotonin depletion does not highly correlate with levels of hyperactivity in animals with electrolytic lesions of the VMT. Indeed, in the present study, no strong correlations were observed between any amine depletion and VMT hyperactivity.

Thus, the chronic hyperactivity observed in the present study may reflect an imbalance in one or more mutually antagonistic systems. Although it is not clear that serotonin is involved, a neuronal system localized in the midline ventral midbrain would seem a likely candidate. Further, the response of VMT-lesioned rats to the locomotor stimulating effects of amphetamine may suggest that the mesolimbic dopamine system is not essential for the amphetamine response, but merely acts in opposition to another inhibitory system. An alternate hypothesis which must be considered would be that the dopamine neurons remaining are adequately mediating the amphetamine response when an inhibitory or antagonistic system has been removed.

Finally, the present documentation of the damage inflicted to several neurotransmitter pathways by electrolytic lesions of the VMT suggests that considerable attention must be paid to such incidental amine manipulation when attempting to conduct behavioral studies utilizing the lesion method.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the skilled technical assistance of Richard Howard, Clifton Johnson and Michie Vane, as well as the contributions of Judith Quinn and Debra Zellner in the preparation of the manuscript.

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