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The Role of Forebrain Dopamine Systems in Amphetamine Induced Stereotyped Behavior in the Rat

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Abstract. The caudate nucleus or the tuberculum olfactorium of the rat was lesioned by bilateral stereotaxic injection of 6-hydroxydopamine. The degree of dopamine depletion was assessed by a sensitive regional dopamine assay and revealed severe depletions in the lesioned areas. The locomotor response to a low dose of *d*-amphetamine was not modified by either lesion. However, the stereotypy response to a high dose of amphetamine was abolished by the caudate lesion. The stereotypy response was not modified by lesion to the tuberculum olfactorium. Neither lesion abolished the stereotypy response to apomorphine. The results therefore demonstrate that amphetamine is an indirect sympathomimetic agent and further emphasize the critical role of the dopaminergic nigrostriatal pathway in amphetamine induced stereotypy.

Key words: Stereotypy — Amphetamine — Caudate Nucleus — Tuberculum Olfactorium — 6-Hydroxydopamine.

Introduction

Psychopharmacological investigations by many researchers have indicated a primary role of central dopaminergic mechanisms in the mediation of amphetamine induced stereotyped behaviors in the rat (Randrup and Munkvad, 1970; Ernst, 1969; Fog *et al.*, 1970; Creese and Iversen, 1972). Fluorescent-histochemical mapping has shown that the major neural pathway in the CNS utilizing dopamine (DA) as a transmitter is the afferent pathway from the substantia nigra to the striatum (Ungerstedt, 1971a; Andén *et al.*, 1966). It has been hypothesized that amphetamine acts, as an indirect sympathomimetic agent, by releasing DA (or inhibiting its reuptake) from the DA terminals of the nigro-striatal pathway and that the resultant increased activity at the DA receptors in the striatum is associated with stereotyped behavior (Ungerstedt, 1971b; Weissman *et al.*, 1966; Randrup and Munkvad, 1966; Stolk and Rech, 1970; Scheel-Kruger, 1972; Taylor and Snyder, 1971).

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In support of this hypothesis, we have previously shown that bilateral chemical lesions, with 6-hydroxydopamine, of the nigro-striatal pathway at the level of the substantia nigra severely reduced the number of DA terminals in the striatum and abolished the stereotyped behaviors normally induced by amphetamine (Creese and Iversen, 1972). As 6-hydroxydopamine selectively damages those neurons which utilize the catecholamines (DA and noradrenaline) as transmitters (Ungerstedt, 1971d; Uretsky and Iversen, 1970), the postsynaptic neurons in the striatum, which are not known to be catecholaminergic, should remain intact. These postsynaptic sites which are normally stimulated by presynaptic release of DA, should now only be activated by DA agonists with direct receptor stimulating properties. In agreement with this hypothesis, the systemic injection of apomorphine, a directly acting DA agonist (Andén *et al.*, 1967), still induced stereotyped behavior in rats in which the nigro-striatal pathway had been lesioned (Creese and Iversen 1973). It would thus appear that an intact nigro-striatal pathway is necessary for the induction of stereotypy by amphetamine and that the behavior is mediated by an increase in dopaminergic activity in the striatum.

However, McKenzie (1972) has shown that bilateral surgical lesions (which are not specific to catecholaminergic neurons) of the tuberculum olfactorium, which also receives a DA input from the mesencephalon, abolished the stereotyped behavior induced by apomorphine whereas a lesion to the caudate nucleus of the striatum did not.

This would indicate that the DA receptors responsible for the mediation of stereotyped behavior are located in the tuberculum olfactorium rather than in the striatum.

In an attempt to reconcile these differing results, the effects of bilateral 6-hydroxydopamine lesion of either the caudate nucleus or the tuberculum olfactorium on the behavioral responses of rats to amphetamine and apomorphine were compared.

Method

Subjects. Forty-eight male albino Wistar rats, mean operative weight 300 g, were housed in groups of three with free access to food and water. The rats were maintained in controlled conditions with a 12 hrs light-dark cycle (8 a. m.—8 p. m.).

Surgery. The rats were anesthetized with Equithesin (3.75 ml/kg). Fifteen rats received bilateral injections of 6-hydroxydopamine into the caudate nucleus of the striatum stereotaxic coordinates AP 7.8, L 3.0, V 5.5 (Peligrino and Cushman, 1967); fifteen rats received bilateral injections of 6-hydroxydopamine into the tuberculum olfactorium using coordinates AP 8.6, L 3.0, V 9.5; six rats received the full sham procedure of vehicle injection into the caudate nucleus and six rats received the full sham procedure of vehicle injection into the tuberculum olfactorium; six rats received no surgical interference. Stereotaxic injections were made from a 5 μl Hamilton syringe through a 30 gauge cannula. The total injection volume was 2 μl on each side, injected over a period of 2 min.

Drugs. 6-Hydroxydopamine hydrochloride (AB Biotec) was dissolved in a vehicle solution of ice-cold, 0.9% saline (pH 4.5) with 1 mg/ml ascorbic acid as an antioxidant. 8 μg 6-Hydroxydopamine (free base) in 2 μl, or an equal volume of vehicle solution was injected on each side. *d*-Amphetamine sulfate (Smith, Kline and French) and apomorphine hydrochloride (McFarlan Smith) were dissolved in 0.9% saline and injected via the intraperitoneal route.

Behavioral Testing. The animals' reponse to drug manipulations was measured in a bank of 12 wire cages (25×40×20 cm), each with two horizontal photocell beams along the long axis, in a room which was masked with white noise and maintained at 22°C. Non-cumulative recordings of photocell beam interruptions, for individual animals, were taken every 10 min in each experimental session.

Low dose levels of amphetamine stimulate locomotor activity in the rat and the beam interruptions recorded in the photocell cages are a reliable measure of the degree of stimulated activity. However, high doses of amphetamine or the administration of apomorphine in the normal rat produce stereotypy in which elements of behavior such as sniffing, licking or gnawing are repeated to the exclusion of other behaviors, particularly active locomotion. This stereotyped behavior could not be quantified reliably by photocell beam interruptions since intense stereotypy with little locomotor activity yielded low counts, while less intense stereotypy associated with a greater degree of locomotor activity might yield high or low counts. A stereotypy rating scale, previously developed from observations of the behavior of normal rats exposed to increasing doses of amphetamine was used (Creese and Iversen, 1973):

0, asleep or stationary; 1, active; 2, predominantly active but with bursts of stereotyped sniffing or rearing; 3, stereotyped activity such as sniffing along a fixed path in the cage; 4, stereotyped sniffing or rearing maintained in one location; 5, stereotyped behavior in one location with bursts of gnawing or licking; 6, continual gnawing or licking of the cage bars.

During the amphetamine and apomorphine studies observations of each animal's behavior were made at 10 min intervals and their stereotypy response rated.

Testing Schedule. After a postoperative recovery period of 3 weeks behavioral testing commenced. Two groups of 12 rats, containing 6 caudate lesioned, 6 tuberculum olfactorium lesioned, and the 12 sham operated rats were run on alternate days, to allow direct comparisons between the lesioned and sham operated animals. The further 9 caudate and 9 tuberculum olfactorium lesioned rats were run on separate occasions. All testing commenced at 10 a.m. The rats were habituated to the photocell cages for 2 hrs on 3 alternate days and their spontaneous activity was measured during these habituation periods. Drug testing was then begun, with the rats being placed in the activity cages 30 min before drug injection to allow activity to stabilize at baseline. The following drug injection schedule was followed, testing on alternate days: saline (1 ml/kg), 1.5 mg/kg *d*-amphetamine, 5 mg/kg *d*-amphetamine, saline (1 ml/kg), apomorphine 1 mg/kg, apomorphine 2 mg/kg.

Biochemical Methods. After behavioral testing was completed six representative caudate lesioned and six representative tuberculum olfactorium lesioned rats and the six control rats were killed by decapitation and the brains rapidly removed, chilled and the caudate nucleus and tuberculum olfactorium dissected out. DA was assayed by a modification of the radiochemical enzymatic procedure of Cuello *et al.* (1973) using rat liver catechol-O-methyl transferase and ^{3}H-S-adenosyl-methionine.

Analysis of Results. Regional assay data were analyzed utilizing the Student's *t*-test, distribution of scores among the stereotypy rating categories using the

Mann-Whitney U Test, and the distribution of photocell beam interruptions with time was subjected to Analysis of Variance. Comparisons between the two lesioned groups were made between the 15 caudate and 15 tuberculum olfactorium lesioned rats, while comparisons between the lesioned and sham operated rats were made between the 6 caudate, 6 tuberculum olfactorium and the 12 respective sham operated which were run at the same time.

Results

Body Weight. The caudate lesioned group lost 11% of their preoperative weight in the 3 days after the lesion. They were then given wet mash to eat and their body weight regained preoperative levels within 13 days. The tuberculum olfactorium lesioned group, however, showed no weight loss and gained weight more rapidly than either of the sham operated groups. At 13 days post lesion the caudate lesion group mean weight was 100% preoperative level, the tuberculum olfactorium lesion group 110% and that of both the sham lesioned groups 105%. These differences were significant ($F = 3.778$; df 3,20,, $P < 0.05$).

Spontaneous Activity. There was no significant difference in the mean activity of either of the lesioned groups ($F = 2.918$; df 1,28) or between the lesioned and sham operate groups ($F = 1.046$; df 3,20) over the 3 habituation periods. The mean total activity of all groups decreased in a similar manner over the 3 habituation periods ($F = 1.775$; df 6,40). There was also no significant difference in the mean activity following saline injection of either lesioned group ($F = 0.450$; df 1,28) or between lesioned and sham operated groups ($F = 1.065$; df 3,20) with respective means for the caudate lesioned tuberculum olfactorium lesioned and their respective sham operates of 31, 34, 41 and 44 counts/10 min.

Amphetamine Induced Activity. There was a significant difference between the mean activity to 5 mg/kg *d*-amphetamine of the caudate lesioned and tuberculum olfactorium lesioned groups ($F = 28.58$; df 1,28; $P < 0.001$). Whereas the caudate lesioned group recorded a mean of 611 beam interruptions per 10 min throughout the session, the tuberculum olfactorium lesioned group recorded a mean of 117 beam interruptions. There was no difference between the two sham operated groups ($F = 0.837$; df 1,10) the sham caudate lesion group recording a mean of 118 beam interruptions and the sham tuberculum olfactorium lesion group recording 154 beam interruptions per 10 min.

The reason for this difference in the activity scores between the caudate lesioned and both the tuberculum lesioned and sham operate groups is clear from Fig. 1. Whereas the caudate lesioned rats maintained constant activity throughout the session, a sharp decrement in beam interruptions over the first 90 min of the session was recorded in the tuberculum olfactorium lesioned group and the sham operates. This corresponded with the appearance of vigorous stereotypy in the tuber-

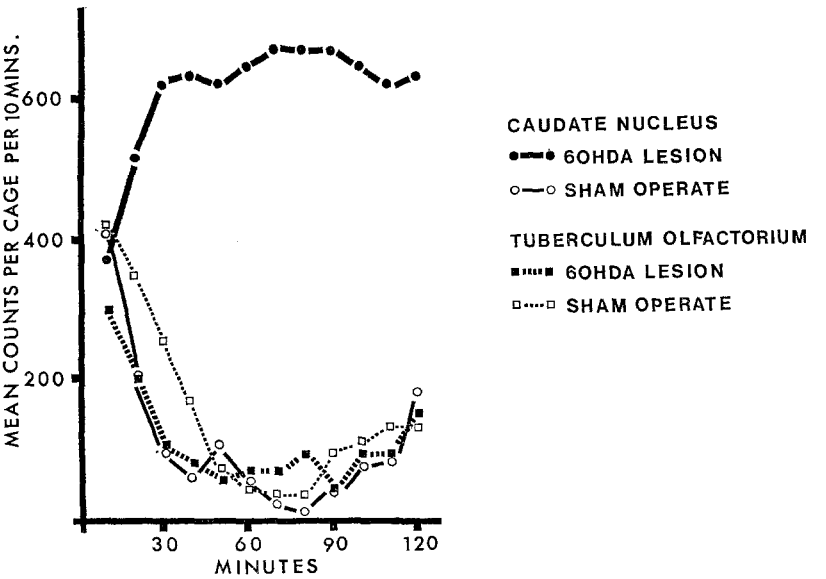

Fig. 1. Activity response to 5 mg/kg *d*-amphetamine: Mean photocell beam interruptions per 10 min for the caudate and tuberculum olfactorium 6OHDA lesioned rats and their sham operated controls. The sharp decrement in beam interruptions during the first 90 min after injection for the tuberculum olfactorium lesioned rats and both sham operate groups corresponded with the appearance of vigorous stereotypy maintained in one location. The caudate lesioned rats showed continuous locomotor and no stereotypy

culum olfactorium lesioned and sham operate rats. The animals sniffed vigorously in one location within the cage thus reducing their number of beam interruptions. The mean stereotypy rating scores over the session were 3.8 for the tuberculum olfactorium lesioned rats, 3.8 for the sham caudate, and 4.0 for the sham tuberculum olfactorium lesioned rats (Fig. 2). The caudate lesioned animals however showed much reduced stereotypy ($P < 0.001$ Mann Whitney U Test), with a mean score on the stereotypy rating scale of 1.6. They continued to show locomotion with only bursts of stereotyped sniffing.

The increased beam interruptions recorded for the caudate lesioned group was associated with the blockage of stereotypy and not due simply to a greater sensitivity to the stimulatory actions of amphetamine. There was no significant difference in the mean locomotor activity to 1.5 mg/kg *d*-amphetamine of the caudate or tuberculum olfactorium lesioned groups ($F = 0.601$; df 1,28) or of the lesioned and sham operated groups ($F = 0.346$; df 3,20) (Fig. 3). The caudate lesioned group recorded a mean of 293, the tuberculum olfactorium lesioned group a mean of

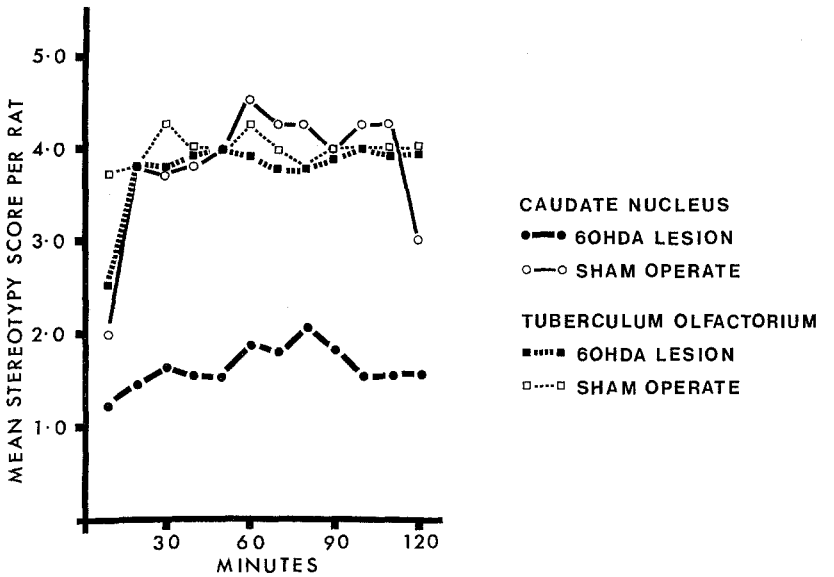

Fig. 2. Stereotypy response to 5 mg/kg *d*-amphetamine: The tuberculum olfactorium 6OHDA lesioned rats and both sham operate groups showed vigorous stereotypy throughout the session while the caudate 6OHDA lesioned rats maintained constant activity

259 beam interruptions per 10 min, with means of 306 and 294 for the respective sham operated groups.

Apomorphine Induced Activity. There was no significant difference between the activity scores to 1 mg/kg apomorphine of either the lesioned groups ($F = 0.338$; *df* 1,28) or the sham operates ($F = 1.799$; *df* 1,10) when compared separately. However, when the matched groups were compared there was a significant difference ($F = 3.428$; *df* 3,20; $P < 0.05$) in the activity scores. The mean activity of the caudate group was 30 beam interruptions per 10 min, the sham caudate lesioned was 64 and both tuberculum olfactorium and sham operates 46. The difference in activity scores of the caudate operated rats was due to the differing ratio of stereotypy to locomotor activity induced in these groups. The caudate lesion group showed a higher level of stereotypy ($P < 0.01$, Mann Whitney U Test) to 1.0 mg/kg apomorphine than the other groups (Fig. 4). The response of the tuberculum olfactorium lesioned group, although not significantly lower than that of the sham operated groups, indicated a diminished apomorphine response. When the matched groups were tested with 2 mg/kg apomorphine the activity responses were not significantly different between any groups ($F = 2.227$; *df* 3,20)

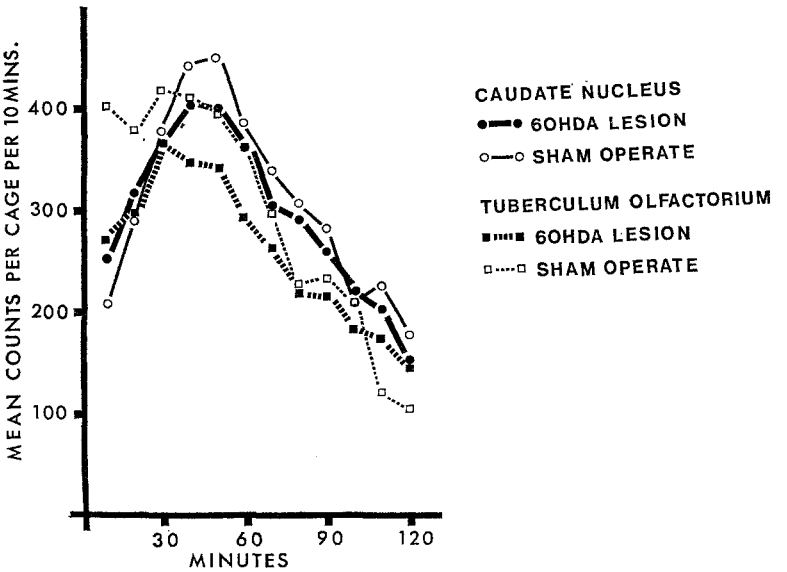

Fig. 3. Activity response to 1.5 mg/kg *d*-amphetamine: Mean beam interruptions per 10 min for the caudate and tuberculum olfactorium 6OHDA lesioned rats and their sham operated controls. There was no significant difference in the activity between the groups

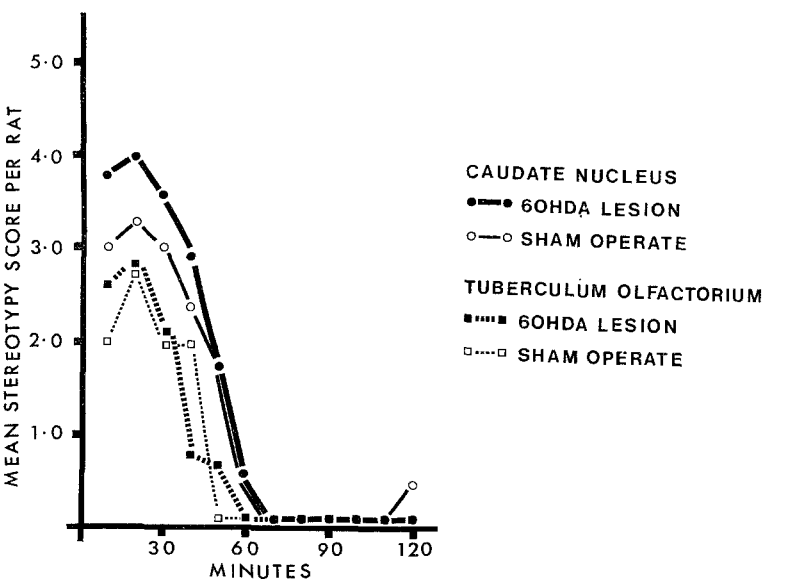

Fig. 4. Stereotypy response to 1 mg/kg apomorphine: All groups showed stereotyped behavior typical of that induced by apomorphine in normal rats. The caudate 6OHDA lesioned rats showed greater stereotypy than the other groups

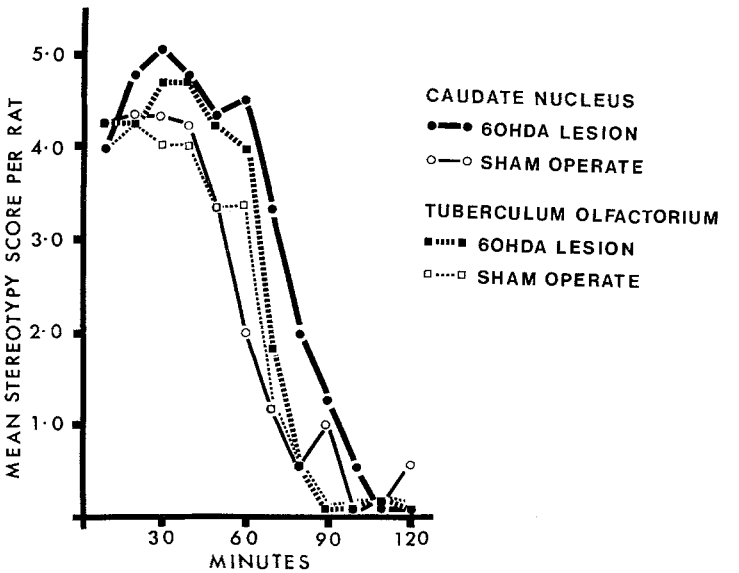

Fig. 5. Stereotypy response to 2 mg/kg apomorphine: All groups showed stereotyped behavior typical of that induced by apomorphine in normal rats and the caudate 6OHDA lesioned rats again were enhanced compared to the other groups

the caudate lesioned group recording a mean of 43 beam interruptions per 10 min the tuberculum olfactorium lesioned group 35 and both sham operated groups 46. Their respective mean stereotypy scores were 2.9, 2.4, 2.1, and 2.1 over the 2 hrs session. The response of the caudate lesioned animals was again significantly higher than that of the other 3 groups ($P < 0.05$, Mann Whitney U Test) (Fig. 5).

Biochemical Results. The regional assay data for DA content is presented in Table 1. Values obtained for the lesioned groups are expressed as percentages of the values from the nonoperated controls. The caudate lesion was very extensive with more than 90% of the caudate DA lost, while the tuberculum olfactorium lesion resulted in a loss of about 45% of its DA input.

Discussion

It is clear from the results of this experiment that a bilateral 6-hydroxydopamine (6OHDA) lesion to the caudate nucleus of the striatum is sufficient to block the stereotyped behavior induced by amphetamine. The biochemical data demonstrate that this blockage of stereotypy is correlated with a dopamine depletion in the striatum rather than the tuberculum olfactorium. If one argues that the caudate lesion blocked

Table 1. Regional dopamine assay data from 6-hydroxydopamine caudate and tuberculum olfactorium lesioned rats ($N = 6$ and 6). Dopamine levels are expressed as percentages of the values determined from the unoperated controls. The control absolute dopamine levels were: caudate, 4.30 ± 0.24 µg/g and tuberculum olfactorium 1.75 ± 0.21 µg/g

Lesion	Regional dopamine level		Stereotypy	
	Caudate %	Tuberculum olfactorium %	Amphetamine	Apomorphine
Caudate	9.3 ± 2.1*	85.7 ± 8.0NS	Blocked	Enhanced
Tuberculum	79.1 ± 10.2NS	56.3 ± 8.0**	Unchanged	Unchanged

* $P < 0.001$ ** $P < 0.01$ NS $P > 0.05$ Student t Test

stereotypy by the spread of 6OHDA to the tuberculum olfactorium, which in any case resulted in only a 15% depletion of DA, one must then ask why the tuberculum olfactorium lesion itself, which resulted in an even greater depletion of DA, did not also block stereotypy.

The conclusion that the dopaminergic mechanisms in the striatum are critical for the appearance of amphetamine stereotypy is supported by our earlier finding that bilateral 6OHDA lesions to the substantia nigra, which resulted in a caudate DA depletion of the same order of magnitude as in this experiment, also blocked amphetamine induced stereotypy. Electrolytic lesion to the striatum has also been shown to reduce or abolish stereotypy induced by amphetamine (Fog, 1970; Naylor and Olley, 1972). This argument is further supported by the induction of stereotyped behavior by implantation or local injection into the caudate nucleus of DA, L-Dopa, apomorphine or amphetamine (Ernst, 1970; Fog and Pakkenburg, 1971; Ungerstedt *et al.*, 1969).

However, in the present study and others in which substantia nigra or caudate lesions have been reported to attenuate stereotypy, it must be borne in mind that dopamine containing neurones or their terminals in forebrain structures in addition to the caudate, may have been involved, (Costall and Naylor, 1974).

The results of the experiments on apomorphine induced stereotypy are also clear. 6OHDA damages the presynaptic amine terminals, leaving postsynaptic receptors intact and should therefore not be expected to abolish responses to direct receptor-activating drugs, such as apomorphine. As expected, neither lesion resulted in the reduction or blockage of apomorphine induced stereotypy, and indeed the removal of the DA input to the striatum increased the behavioral response to apomor-

phine, a result not unexpected since a behavioral supersensitivity to DA agonists has been previously demonstrated after DA terminal degeneration associated with 6OHDA lesions (Ungerstedt, 1971c; Uretsky and Shoenfeld, 1971; Shoenfeld and Uretsky, 1972; Creese and Iversen, 1973).

However, while these results are internally consistent and verify that DA mechanisms in the striatum mediate amphetamine and apomorphine induced stereotypy, they are in disagreement with McKenzie's findings. Using electrolytic lesions of forebrain regions to remove both DA receptors and DA terminals, he found that tuberculum olfactorium lesions abolished apomorphine induced stereotypy whereas caudate lesions did not (McKenzie, 1972).

Fog *et al.* (1970) have previously shown that the size of the striatal lesion is positively correlated with the degree of blockage of amphetamine induced stereotypy and Divac (1972) has shown that a lesion of up to about 80% of the striatum (estimated by anatomical techniques) did not alter amphetamine and apomorphine stereotypy. It is therefore possible that McKenzie's caudate lesions simply failed to remove a sufficient number of the DA receptors.

The remaining discrepancy, notably that removal of DA receptors from the tuberculum olfactorium abolished apomorphine induced stereotypy in McKenzie's study whereas in the present study removal of presynaptic DA terminals in this area failed to block amphetamine stereotypy, is more difficult to explain. McKenzie concludes that DA systems in the tuberculum olfactorium are essential for apomorphine stereotypy to occur. The present results have only limited bearing on this point as the 6OHDA lesion resulted in less than 50% loss of DA terminals. Equivalent damage to the caudate nucleus would also fail to block stereotypy and therefore our results with the tuberculum olfactorium lesion do not definitively rule out a role for this structure in the circuitry mediating stereotypy. Proof that the striatum is the only site of DA systems involved in stereotypy would rest on the demonstration that virtually total DA depletion in the tuberculum olfactorium failed to abolish amphetamine stereotypy. This we have not shown and in its absence McKenzie's results indicate that damage of the tuberculum olfactorium prevents stereotypy from emerging after direct activation of DA receptors. Some of those receptors may be in the tuberculum olfactorium itself, but this structure could equally contribute to the circuitry involved in the translation of dopamine receptor stimulation in the striatum into overt behavior. The precise contribution of the tuberculum olfactorium to stereotyped behavior remains to be evaluated but regardless of this outcome, it is clear that a crucial set of DA receptors involved in stereotyped behavior lie in the caudate nucleus.

It is of interest that the caudate lesion disrupted food and water intake patterns of these rats, an effect which has been found after substantia nigra lesions (Simpson and Iversen, 1971; Iversen, 1971) and also lesion to the lateral hypothalamus (Teitelbaum and Epstein, 1962). This results would support Ungerstedt's (1971e) contention that the "lateral hypothalamic syndrome" is due, in part, to the removal of the DA input to the striatum, rather than damage to specific mechanisms within the lateral hypothalamus.

The present results do not rule out the modulatory influence of other brain areas or neurotransmitters on drug induced stereotyped behavior, but serve to re-emphasize the critical role of the dopaminergic nigro-striatal pathway in amphetamine induced stereotypy.

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