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Attenuation of amphetamine-induced motor stimulation and stereotypy by 6-hydroxydopamine in the rat

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Summary

1. In accord with previous reports, intraventricular administration of 6-hydroxydopamine (250 μg) to rats did not influence spontaneous locomotor activity. Neither was the stereotyped behaviour seen after high doses of (+)-amphetamine (5 mg/kg) changed by this treatment. Increases in motor activity induced by (+)-amphetamine (0·5 and 1·0 mg/kg) were significantly reduced after 6-hydroxydopamine.

2. When 6-hydroxydopamine (250 μg) was administered to tranylcypromine (5 mg/kg) pretreated animals, spontaneous activity was significantly reduced. The stimulant effects of (+)-amphetamine (0·5 and 1·0 mg/kg) were completely abolished and amphetamine stereotypy (5·0 mg/kg) was absent or reduced after this treatment.

3. Bilateral injections of 6-hydroxydopamine (10 μg) into the substantia nigra abolished the more pronounced features of amphetamine stereotypy. However, although significantly reduced, amphetamine-induced locomotor stimulation was observed in these animals. Spontaneous activity was also reduced.

4. These observations suggest that dopaminergic nigro-striatal neurones mediate some of the stimulant effects of amphetamine as well as being of critical importance in amphetamine-induced stereotypy. However, other catecholaminergic neurones also appear to be involved in amphetamine motor stimulation. The results are consistent with the view that amphetamine exerts its behavioural effects indirectly through its action on brain catecholamines.

Introduction

There is considerable evidence which suggests that (+)-amphetamine is an indirectly-acting sympathomimetic agent whose stimulant actions are mediated by brain dopamine and noradrenaline. Thus, agents which interfere with the synthesis of these catecholamines have been shown to attenuate the stimulant properties of the drug (Weissman & Koe, 1965; Hanson, 1967; Stolk & Rech, 1970; Mayer & Ebyl, 1971). In addition, (+)-amphetamine increases the synaptic release of catecholamines and inhibits their subsequent re-uptake (McKenzie & Szerb, 1968; Carr & Moore, 1970; Farnebo, 1971).

6-Hydroxydopamine (6-OHDA) can produce a selective destruction of catecholaminergic nerve endings and cell bodies in the central nervous system (Bloom, Algeri, Groppetti, Revuelta & Costa, 1969; Breese & Traylor, 1970; Uretsky & Iversen, 1970; Descarries & Saucier, 1972; Fibiger, Pudritz, McGeer & McGeer,

1972; McGeer, Fibiger, McGeer & Brooke, 1972). When administered into the cerebrospinal fluid the drug generally has a greater toxic action on noradrenergic than on dopaminergic neurones but if monoamine oxidase is inhibited an equally profound effect can be obtained on dopamine-containing neurones (Breese & Traylor, 1971; Fibiger, Lonsbury, Cooper & Lytle, 1972). In theory, 6-OHDA should be of considerable use in defining the role of catecholaminergic neurones in amphetamine mediated behaviour. Surprisingly, it has been observed that intraventricular pretreatment with large doses of 6-OHDA fails to attenuate amphetamine motor stimulation, despite a reduction of brain catecholamines by 75–80% (Evetts, Uretsky, Iversen & Iversen, 1970). This finding is in accord with other reports which have described a general lack of long-lasting behavioural changes, except for increased irritability, after intraventricular 6-OHDA (Burkhard, Jalfre & Blum, 1969; Laverty & Taylor, 1970; Schoenfeld & Zigmond, 1970; Taylor, Snyder & Laverty, 1970; Nakamura & Thoenen, 1972). Recently, in a study of the early behavioural effects of 6-OHDA it was observed that when rats are pretreated with a monoamine oxidase inhibitor (MAOI), intraventricularly administered 6-OHDA produces behavioural changes including aphagia, adipsia, and reduced spontaneous locomotor activity (Fibiger *et al.*, 1972a). In the present experiments therefore the effects of 6-OHDA on amphetamine-induced locomotor stimulation and stereotyped behaviour were re-examined. In addition, as MAO inhibition tends to increase the effect of 6-OHDA on dopaminergic neurones (Breese & Traylor, 1971), an attempt was made to evaluate the role of the dopaminergic nigro-striatal system in these behavioural effects.

Methods

Male Wistar rats (Woodlyn Farms, Ontario, Canada) weighing 350–400 g at the start of the experiment were used. Animals were injected intraventricularly with 250 μg of 6-OHDA hydrobromide (dose expressed as the free base) half an hour after an intraperitoneal injection of either tranylcypromine sulphate (5 mg/kg, expressed as the salt) or 0·9% w/v NaCl solution (saline). The intraventricular injection was made under light ether anaesthesia by the method of Noble, Wurtman & Axelrod (1967). The 6-OHDA was injected in a volume of 25 μl and was dissolved in saline containing ascorbic acid (1 mg/ml). Control animals were treated identically except that the intraventricular injection contained no 6-OHDA. Half of the control animals were pretreated with tranylcypromine sulphate (5 mg/kg) and half received injections of saline.

In another group of animals, 10 μg of 6-OHDA was injected stereotaxically into each substantia nigra in a volume of 2 μl by the method of Fibiger *et al.* (1972b). The injection co-ordinates according to Konig & Klippel (1963) were A.+2·2 mm, L.+2·0 mm, and D.V.−2·5 mm and were verified histologically in pilot experiments.

After the surgical procedure the animals were housed individually and their food and water intake was recorded daily. Those animals that became aphagic were fed intragastrically twice daily with a solution of Esbilac (Borden Co.) until they were able to maintain themselves on Purina rat chow.

Following recovery of feeding, the animals were tested as follows:

(1) *Spontaneous locomotor activity* Each animal was placed in a circular cage (14 inches in diameter) with 2 photocells located at 90° to each other. The cages

were located in a dark room with a 70 decibel white noise background. The number of photobeams broken over a 1 h period was automatically recorded on mechanical counters located in another room. This test was conducted 4 weeks after the 6-OHDA administration.

(2) *Locomotor response to (+)-amphetamine* Each animal was placed in the photocell cage for 1 h, after which it was injected intraperitoneally with (+)-amphetamine sulphate (0·5 or 1·0 mg/kg, expressed as the salt), or distilled water in a volume of 1 ml/kg. The subsequent activity was then measured for 1 hour. Three days separated each amphetamine test. These tests were conducted 5 weeks after the 6-OHDA treatment.

(3) *Stereotyped behaviour in response to (+)-amphetamine* Animals were injected intraperitoneally with 5 mg/kg of (+)-amphetamine and returned to their home cages from which food and water were removed. The resulting behaviour was recorded at half hour intervals for 3 h by two observers using a modification of the rating scale of Naylor & Olley (1972): 0=normal behaviour; 1=exploratory behaviour, discontinuous sniffing; 2=continuous sniffing; 3=small, compulsive head-neck movements; 4=licking or biting the wires of the cage. This test was conducted 10 weeks after the 6-OHDA administration. After the behavioural experiments were completed, the animals were killed by cervical fracture and the brains were dissected on ice into the corpora striata, hypothalamus and midbrain as described by Fibiger & McGeer (1971). Tyrosine hydroxylase activity was assessed to determine the extent of the damage to catecholaminergic neurones in each of the brain areas by the method of McGeer, Gibson & McGeer (1967). In previous reports the extent of the decrease in tyrosine hydroxylase activity after 6-OHDA has been found to correspond closely with other measures of catecholaminergic neurone function which are impaired by 6-OHDA (Bell, Iversen & Uretsky, 1970; Breese & Traylor, 1970; Uretsky & Iversen, 1970). The results were analysed statistically by analysis of variance and Student's *t* test.

Results

General observations

Because no significant differences were observed with any of the tests between the controls receiving saline and those receiving tranylcypromine, these animals were treated as one group.

Intraventricular injections of 6-OHDA increased the irritability of animals whether or not they were pretreated with tranylcypromine. Most of these animals could be made to vocalize simply by touching them on the back. When handled and injected intraperitoneally, these animals were again very vocal and aggressive. This behaviour persisted throughout the 3 month duration of the study. The control animals and the group in which 6-OHDA had been injected bilaterally into the substantia nigra never showed these responses. The latter group in fact appeared to be even more docile than the controls.

Both the substantia nigra-injected group and the group given 6-OHDA with tranylcypromine pretreatment became aphagic and adipsic. In most animals, recovery of food and water intake occurred within 10 days. In some animals, however, aphagia and adipsia persisted for the duration of the experiment. These animals were not used in the motor tests because the nutritive state of rats can

greatly influence the stimulant effect of amphetamine (Campbell & Fibiger, 1971; Fibiger, Trimbach & Campbell, 1972c). None of the animals in the control group or in the group receiving intraventricular 6-OHDA without MAO inhibition became aphagic or adipsic. A more complete account of the deficits in food and water regulation in these different groups has been given elsewhere (Fibiger & Zis, 1973).

Spontaneous locomotor activity

The results of this test are seen in Table 1. Highly significant differences in spontaneous locomotor activity were observed between the groups ($F=26{\cdot}5$, $df=3$, 36, $P<0{\cdot}01$). The only animals which did not differ significantly from the controls were the intraventricular 6-OHDA group. The 6-OHDA+MAOI group displayed the lowest value of spontaneous activity and was significantly less active than the substantia nigra-injected group ($P<0{\cdot}01$) although both groups were less active than the controls ($P<0{\cdot}01$).

TABLE 1. *Effect of 6-hydroxydopamine (6-OHDA) on spontaneous locomotor activity*

Group†	Activity $\bar{X}\pm$S.D.	% of control
Controls	278±66	100
Nigral 6-OHDA	187±41*	67
Intraventricular 6-OHDA	256±84	92
Intraventricular 6-OHDA+MAOI	63±30*	23

* Significantly different from control group $P<0{\cdot}01$. † Nigral 6-OHDA animals received an injection of 6-OHDA (10 μg in 2 μl) into each substantia nigra. Intraventricular 6-OHDA animals received an injection of 6-OHDA (250 μg in 25 μl) into the right lateral ventricle 30 min after an i.p. saline injection. Intraventricular 6-OHDA and MAOI animals received an injection of 6-OHDA (250 μg in 25 μl) into the right lateral ventricle 30 min after tranylcypromine (5 mg/kg, intraperitoneally). Control animals received intraventricular injections of the vehicle (25 μl) 30 min after tranylcypromine (5 mg/kg) or saline intraperitoneally.

Amphetamine-induced motor stimulation

With the exception of the 6-OHDA+MAOI group, all groups showed a dose-dependent increase in locomotor activity in response to (+)-amphetamine ($P<0{\cdot}01$). The lack of an effect of (+)-amphetamine on the 6-OHDA+MAOI group is evident in Figure 1. Although the substantia nigra-injected group and the 6-OHDA group increased their activity in response to amphetamine, when this was compared to controls the extent of the increase was significantly attenuated both at 0·5 mg/kg ($P<0{\cdot}05$) and 1·0 mg/kg ($P<0{\cdot}01$). The 6-OHDA+MAOI group was significantly less active than the substantia nigra-injected and the 6-OHDA group at both doses of (+)-amphetamine ($P<0{\cdot}01$).

Amphetamine-induced stereotypy

The results of this experiment are seen in Table 2. Stereotypy differed significantly between the groups ($F=12{\cdot}01$, $df=3$, 36, $P<0{\cdot}01$). Intraventricular 6-OHDA did not significantly influence the mean stereotypy score. When 6-OHDA was administered to tranylcypromine pretreated animals, however, the mean response was significantly decreased ($P<0{\cdot}01$). Bilateral injection of 6-OHDA into the substantia nigra also significantly decreased the mean amphetamine stereotypy score.

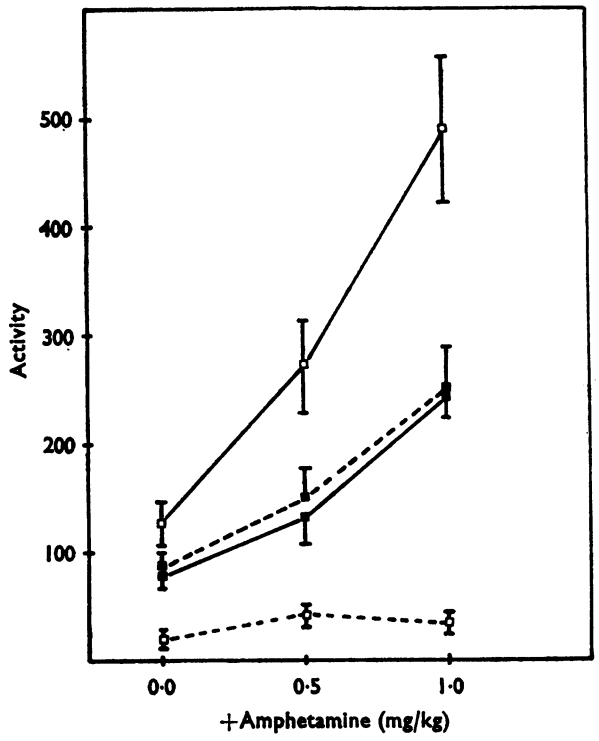

FIG. 1. The effect of (+)-amphetamine on locomotor stimulation after various treatments with 6-hydroxydopamine (for details see **Methods** and Table 1). Animals were adapted to the cages for 1 h and then injected intraperitoneally with (+)-amphetamine after which locomotor activity was measured for 1 hour. Each point represents the mean of 10 animals (±S.E.M.). □——□, Controls; ■——■, nigral 6-OHDA; ■- - -■, intraventricular 6-OHDA; □- - -□, intraventricular 6-OHDA+MAOI.

TABLE 2. *Effect of 6-hydroxydopamine (6-OHDA) on amphetamine (5 mg/kg)-induced stereotypy*

Group	Stereotypy score 0	1	2	3	4	Mean stereotypy score $\bar{X}$±S.D.	% of control
Control	0	0	3·3	78·3	18·3	3·2±0·3	100
Nigral 6-OHDA	20·0	15·0	65·0	0	0	1·5±0·7*	47
Intraventricular 6-OHDA	0	0	18·3	53·3	28·3	3·0±0·5	94
Intraventricular 6-OHDA+MAOI	45·0	13·3	8·3	15·0	18·3	1·4±1·4*	44

The data represent the frequency (expressed as a percentage of the total observations) that each group spent in each stereotypy category as scored by a modification of the method of Naylor & Olley (1972).
* Significantly different from control group, $P<0.01$.

TABLE 3. *Effect of 6-hydroxydopamine (6-OHDA) on tyrosine hydroxylase activity*

Group	Midbrain $\bar{X}$±S.D.	% Control	Hypothalamus $\bar{X}$±S.D.	% Control	Corpus striatum $\bar{X}$±S.D.	% Control
Controls	19·5±2·5	100	16·5±2·4	100	96·7±7·4	100
Nigral 6-OHDA	6·6±2·5*	34	11·3±2·2*	68	7·2±4·6*	7
Intraventricular 6-OHDA	8·6±1·5*	44	11·3±1·7*	68	46·1±9·2*	48
Intraventricular 6-OHDA+MAOI	2·3±0·8*	12	6·8±1·7*	41	4·7±1·6*	5

Tyrosine hydroxylase activity was measured in each area by the method of McGeer, Gibson & McGeer (1967) and is expressed as (nmol DOPA/g tissue)/hour. * Significantly different from control group, $P<0.01$.

Tyrosine hydroxylase (Table 3)

(a) *Midbrain* The groups differed significantly in their midbrain tyrosine hydroxylase activity ($F=136{\cdot}7$, $df=3, 36$, $P<0{\cdot}01$). All experimental groups showed significantly lower activity than the controls ($P<0{\cdot}01$). In addition, each of the experimental groups differed significantly from each other ($P<0{\cdot}05$).

(b) *Hypothalamus* The groups differed significantly in the tyrosine hydroxylase activity in the hypothalamus ($F=26{\cdot}8$, $df=3, 36$, $P<0{\cdot}01$). All experimental groups were significantly different from the control group ($P<0{\cdot}01$). The intraventricular 6-OHDA+MAOI group was significantly lower than the other two experimental groups ($P<0{\cdot}01$).

(c) *Striatum* The difference between the groups in striatal tyrosine hydroxylase activity was highly significant ($F=453$, $df=3, 36$, $P<0{\cdot}01$). The three experimental groups were significantly lower than the control group ($P<0{\cdot}01$). The substantia nigra-injected and the intraventricular 6-OHDA+MAOI groups were not significantly different but both were lower than the intraventricular 6-OHDA group ($P<0{\cdot}01$).

Discussion

Spontaneous locomotor activity

These experiments are in general accord with the theory that catecholaminergic neurones are involved in the mediation of spontaneous motor activity. In agreement with previously published results (Burkhard *et al.*, 1969 ; Evetts *et al.*, 1970 ; Fibiger *et al.*, 1972a), it was evident that 6-OHDA by itself did not significantly influence this behaviour, despite a reduction of tyrosine hydroxylase activity by some 50%. When 6-OHDA was administered intraventricularly to animals pretreated with a MAO inhibitor a very significant decrease in spontaneous activity occurred which was accompanied by a more potent action on tyrosine hydroxylase activity in all three areas of brain investigated. The fact that very large changes in tyrosine hydroxylase activity were required to produce decreases in spontaneous activity suggests that the catecholaminergic systems which subserve this behaviour are normally present in excess of the requirement for the maintenance of normal behavioural function, and only when they are reduced to a critical value does disruption of this behaviour become manifest. Thus, the relation between spontaneous exploratory activity and brain catecholaminergic neurones is not linear. Alternatively, inhibition of MAO activity in the brain makes possible an effect of 6-OHDA which is absent or insignificant in animals in which the activity of this enzyme is not inhibited.

The spontaneous activity of the group in which 6-OHDA was injected into the substantia nigra was also significantly less than controls suggesting that the nigrostriatal system is involved in this behaviour. The effect was significantly less than was found in the intraventricular 6-OHDA+MAOI group, indicating that other catecholaminergic neurones are also important in spontaneous motor activity. This conclusion is supported by the fact that although the injection of 6-OHDA into the substantia nigra produced a decrease in striatal tyrosine hydroxylase activity which was of approximately equal magnitude to that observed in the intraventricular 6-OHDA+MAOI group, the two groups differed significantly in the spontaneous activity test. The two groups did, however, differ significantly in hypothalamic and midbrain tyrosine hydroxylase activity suggesting that catechol-

aminergic neurones in these and other areas may contribute to spontaneous locomotor activity. Previous reports have proposed that both noradrenergic and dopaminergic neuronal systems may be important in spontaneous and exploratory motor activity (Fuxe, Hökfelt & Ungerstedt, 1970; Svensson & Waldeck, 1970).

It is noteworthy that Iversen (1971) did not observe a significant effect on spontaneous locomotor activity after bilateral electrolytic lesions of the substantia nigra. While differences in procedure may account for this discrepancy, it appears more likely that the failure to obtain more than a 50% decrease in striatal tyrosine hydroxylase with electrolytic lesions was the critical variable. In the present experiments spontaneous activity was unchanged after a 50% loss of striatal tyrosine hydroxylase activity (intraventricular 6-OHDA group, Tables 1 and 3). Electrolytic lesions of the substantia nigra have been found to be unreliable and only partially effective in this and other laboratories (Poirier, Singh, Boucher, Bouvier, Olivier & Larochelle, 1967; Faull & Laverty, 1969; Poirier, Bedard, Boucher, Bouvier, Larochelle, Olivier, Parent & Singh, 1969). The present findings and the above conclusion are consistent with Ungerstedt's observations (1971) that bilateral injections of 6-OHDA into the substantia nigra caused, after a number of days, a hypokinetic syndrome the magnitude of which depended upon the degree of loss of striatal dopamine.

Amphetamine-induced motor stimulation

Evetts *et al.* (1970) found that after intraventricular 6-OHDA (2×250 μg), there was a tendency for amphetamine to produce a smaller absolute increase in locomotor activity compared with controls. However, this tendency just failed to reach statistical significance. The present results confirm this trend and show that under the present experimental conditions amphetamine stimulation was significantly ($P<0{\cdot}01$) attenuated by intraventricular 6-OHDA (250 μg). The failure of Evetts *et al.* (1970) to obtain a significant inhibition of amphetamine excitation may have been due to differences in procedure. In the former study, activity was recorded for 10 min, 55 min after an intraperitoneal amphetamine injection. The present procedure recorded activity for 60 min immediately after an intraperitoneal injection which followed a 60 min adaptation period. It is possible that the amphetamine-induced activity scores recorded by Evetts *et al.* (1970) were artificially inflated by, or interacted with, exploratory spontaneous activity which would be present during a 10 min recording period (despite daily adaptation) and that this may have obscured differences in the response to amphetamine. As was pointed out above, spontaneous activity is not influenced by intraventricular 6-OHDA (Table 1 and Burkhard *et al.*, 1969; Evetts *et al.*, 1970). The nature of the interaction between spontaneous exploratory behaviour and amphetamine motor stimulation is not known.

After 6-OHDA was given intraventricularly in a tranylcypromine pretreated animal there was a complete absence of amphetamine excitation (Fig. 1). It should be noted that tyrosine hydroxylase activity was significantly less in all three areas measured in this group than in the intraventricular 6-OHDA without MAO inhibition group (Table 3) making it impossible to focus on any one area as being critical in this phenomenon. That the nigro-striatal system is only partly responsible for amphetamine stimulation is indicated by the fact that although the extent of the decrease in striatal tyrosine hydroxylase activity was similar in the group injected

with 6-OHDA into the substantia nigra and the intraventricular 6-OHDA + MAOI group, the stimulant response to (+)-amphetamine was significantly less ($P<0{\cdot}01$) in the latter group. This conclusion is in accord with other studies which suggest that both noradrenergic and dopaminergic mechanisms are of importance in the stimulant effects of amphetamine (Svensson, 1970; Ungerstedt & Arbuthnott, 1970; Mayer & Ebyl, 1971). It should be noted, however, that injections of 6-OHDA into the substantia nigra produced significant decreases in hypothalamic tyrosine hydroxylase activity. This decrease may have been caused by diffusion of the drug from the injection site to the hypothalamus, destruction of ascending axons of noradrenergic neurones which lie medial to the substantia nigra, or it may represent loss of enzyme activity normally found in the nigro-striatal axons which pass through the hypothalamus. Regardless of which of these factors decreased hypothalamic tyrosine hydroxylase activity, this finding suggests the possibility that the changes in the hypothalamus may have been the basis of the attenuation of amphetamine-induced locomotor stimulation. The fact that electrolytic lesions of the substantia nigra reduce the stimulant effects of amphetamine (Iversen, 1971; Fibiger & Zis, unpublished observations) but do not decrease hypothalamic tyrosine hydroxylase activity (Fibiger & Zis, unpublished observations) argues against this possibility. The present results indicate that intraventricular 6-OHDA administered to MAO-inhibited animals destroys the neuronal basis of amphetamine excitation of which the nigro-striatal system may be but one component.

Amphetamine-induced stereotypy

The corpus striatum has been postulated as an important structure for the mediation of amphetamine stereotypy on the basis of a number of experimental approaches (Ernst & Smelik, 1966; Ernst, 1967; Cools & van Rossum, 1970; Fogg, Randrup & Pakkenberg, 1970). The present results are in general accord with this hypothesis. The group injected with 6-OHDA in the substantia nigra and the intraventricular 6-OHDA+MAOI group showed similar reductions in the mean stereotypy score compared with the controls (Table 2) and both groups were depleted of striatal tyrosine hydroxylase activity to about the same extent (Table 3).

Although the mean stereotypy scores of the substantia nigra 6-OHDA group and the intraventricular 6-OHDA+MAOI group were similar, it is apparent from Table 2 that the response was more variable in the latter group. Three animals in the group of 10 were responsible for all of the scores of 3 and 4 recorded for this group. As these three animals showed similar changes in tyrosine hydroxylase activity to the remainder of the group, the reason for this observation is not apparent. However, the responses scored as 3 and 4 in these animals were qualitatively different from controls in that they lacked the vigour, the intense compulsive nature, and the body movements which were present in the control group. The mean of the remaining 7 animals in the intraventricular 6-OHDA and MAOI group was $0{\cdot}59 \pm 0{\cdot}52$, which is significantly lower than the substantia nigra 6-OHDA group ($P<0{\cdot}05$). This suggests that catecholaminergic neurones, other than those in the nigro-striatal system may be involved in some aspects of what is regarded as amphetamine-induced stereotyped behaviour. In particular, continuous sniffing and exploratory behaviour were still evident in the substantia nigra 6-OHDA group whereas the small compulsive head movements, gnawing and licking were abolished. The presence of exploratory and continuous sniffing behaviour is consistent with

the finding that the stimulant effects of amphetamine were attenuated but not abolished in the nigral 6-OHDA group (Fig. 1), and suggests that these effects may be more a reflection of the stimulant effects of the drug than those related to stereotyped behaviour. If this is the case, the data confirm the importance of dopaminergic nigro-striatal neurones in amphetamine-induced stereotypy.

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