*Br. J. Pharmac.* (1973), **49**, 316–321.

# Possible modulating influence of frontal cortex on nigro-striatal function

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## Summary

1. After administration of (+)-amphetamine, rats with unilateral ablations of the frontal cortex rotated either ipsilaterally or contralaterally as a function of time after surgery.

2. At early postoperative intervals (1–7 days), rotation was towards the side of the lesion.

3. At later times (15–30 days), rotation was towards the intact side.

4. Repeated testing with amphetamine appeared to slow the time-course of changes in rotational behaviour.

5. These results suggest that a dopaminergic nigro-striatal system is modulated by the frontal cortex and that unilateral removal of the latter produces a denervation supersensitivity of the former.

## Introduction

Ipsilateral turning and rotational behaviour in rats has been reported to follow unilateral lesions of either the substantia nigra or the striatum (Ungerstedt, 1971b). This behaviour is potentiated by amphetamine (Ungerstedt, 1971b) and elicited by amphetamine (Christie & Crow, 1971 ; Ungerstedt, 1971b ; Naylor & Olley, 1972) when rats have recovered from the tendency to rotate spontaneously. Histofluorescent data (Ungerstedt, 1971b, 1971c) have indicated that the basis for this rotational behaviour is an imbalance between the two dopaminergic systems ipsilateral and contralateral to the lesion, respectively. Amphetamine apparently stimulates the intact nigro-striatal system and enhances the imbalance (Ungerstedt, 1971b). Evidence has also been presented to imply that supersensitivity of the denervated striatum in rats with unilateral substantia nigra lesions mediates the contralateral rotational behaviour induced by drugs directly stimulating dopaminergic receptors in the striatum (Ungerstedt, 1971c). Although the only described dopaminergic input to the striatum of the rat ascends from the substantia nigra (Ungerstedt, 1971a), a descending system of fibres originating in the rostral frontal cortex and distributing through the caudate and pallidum has also been described (Knook, 1966). This latter system, though not dopaminergic, may modulate dopaminergic functions of the striatum. Similar behavioural deficits resulting from lesions of the frontal cortex and the caudate

have been noted (Divac, Rosvold, & Szwarcbart, 1967). By use of the rotation paradigm, the present investigation sought to determine how lesions of the frontal cortex affected behaviour supposedly indicative of dopaminergic striatal function.

## Methods

Forty naive female Sprague-Dawley albino rats were used; they were approximately three months old at the beginning of the experiment. Sixteen rats received unilateral ablations of the frontal cortex, twelve rats received unilateral ablations of the posterior cortex and twelve rats received sham unilateral frontal surgery. Alternate rats of each group received left and right-sided surgery, respectively. All surgery was conducted under methohexital anaesthesia. A scalp incision was made along the midline of the head and subcutaneous tissue was deflected. With the use of a dental drill, a unilateral burr hole, 5 mm in diameter, was made in the skull. For rats with frontal cortex lesions or sham operations, the burr hole was located 0·5 mm anterior and lateral to bregma. For rats with posterior cortex lesions, the burr hole was located 0·5 mm anterior and lateral to lambda. The burr hole alone constituted the sham operation. Either the frontal or posterior cortex was removed under a dissecting microscope by suction through a 20 gauge needle. All operations were completed by closing the wound with 11 mm wound clips.

Following their use in the experiment, all rats were killed and perfused with 10% formalin. Their brains were removed and immersed in 10% formalin for a week before frozen sections (40 $\mu$m, stained with Luxol blue and cresyl violet) were made and histological examination was conducted.

The rotation apparatus was modelled after one described by Ungerstedt (1971b, 1971c). The 'rotometer' consisted of a half sphere 12 inches in diameter made out of white opaque Plexiglass within which the rat rotated. A light harness was placed around the chest of the rat. The harness was attached to a steel wire which in turn was attached to a cam and a microswitch situated one diameter from the floor of the sphere on its axis. The latter was accomplished by mounting the microswitch on top of another twelve inch half sphere and placing the two halves together. The entire apparatus was therefore a complete 12 inch hollow opaque sphere. Each full turn of the rat closed the microswitch; left and right turns were recorded separately on Sodeco counters. The experimenter noted the direction of the rotation by observing which way (clockwise and counter-clockwise) the cam moved. Rotation was always measured for 5 min beginning 30 s after a rat was placed in the apparatus.

Rats with each kind of operative treatment were assigned randomly to one of four experimental conditions ($n$=4, 3 and 3 for frontal, posterior and sham groups, respectively, of each condition) (1) rats were tested 1, 3, 7, 15 and 30 days after surgery, (2) rats were tested only at 7 days after surgery, (3) rats were tested only at 15 days after surgery and (4) rats were tested only at 30 days after surgery. All testing entailed two 5 min sessions 3 h apart. Saline (0·1 ml) was administered i.p. 30 min before the first session and (+)-amphetamine sulphate (5 mg/kg) was administered i.p. 30 min before the second session. The dose of amphetamine employed was based on previous studies (Ungerstedt, 1971b; Christie & Crow, 1971).

**Results**

In all cases, histological study of the rat brains showed that the major area of destruction was confined to the cortex. Only rarely was subcortical white matter included in the lesion ; structures below the corpus callosum were never damaged. The major area of frontal cortex destroyed extended rostrally to the tip of the frontal pole and caudally to the anterior limb of the corpus callosum. The major area of posterior cortex destroyed extended caudally to the occipital pole and rostrally 5 mm anterior to the occipital pole.

Figures 1 and 2 show changes in ipsilateral and contralateral rotational behaviour as a function of time after surgery. In Fig. 1, the same rats were used at all time points whereas in Fig. 2, different rats were used at each time point. The most unequivocal result was that rats with either posterior cortical lesions or with sham surgery showed no significant directional tendency to rotate ; such turns as occurred were generally incomplete and in both directions regardless of the time point and drug condition. Rats with frontal cortical lesions, however, showed definite rotational behaviour which varied as a function of time after

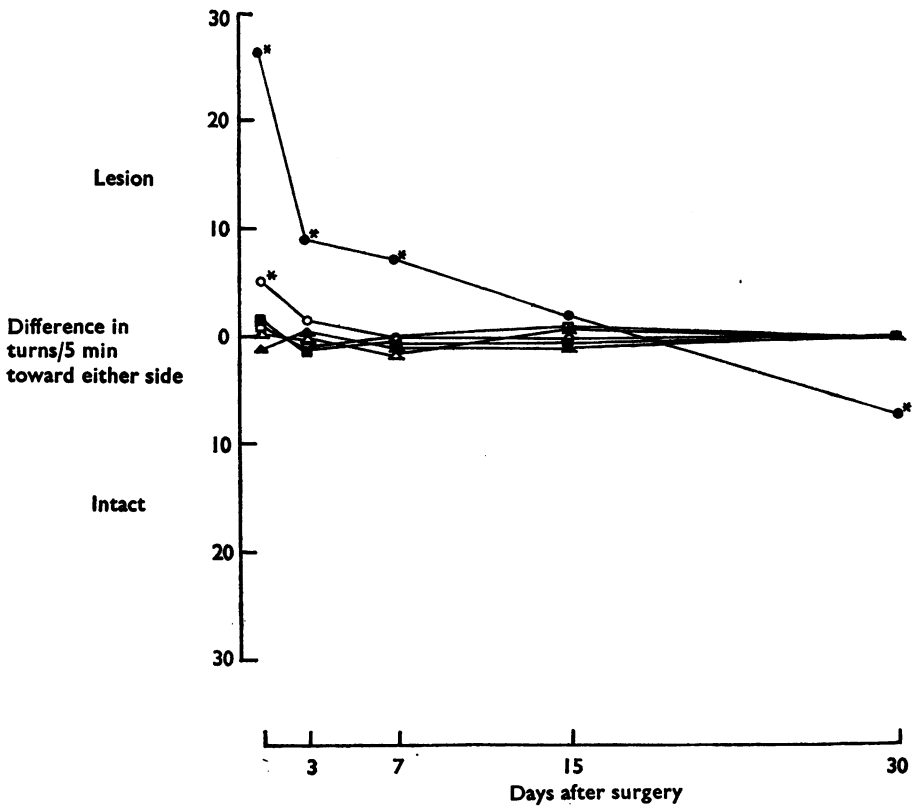


FIG. 1. Time-dependent changes in rotational behaviour following unilateral ablation of frontal cortex ; the same rats were used at all time points. A significant ($P<\cdot05$, $t$ test) difference between ipsilateral and contralateral turns is indicated by an asterisk. ●——● rats with frontal cortical lesions given amphetamine ; ○——○ rats with frontal cortical lesions given saline ; ▲——▲ rats with posterior cortical lesions given amphetamine ; △——△ rats with posterior cortical lesions given saline ; ■——■ sham operated rats given amphetamine □——□ sham operated rats given saline.

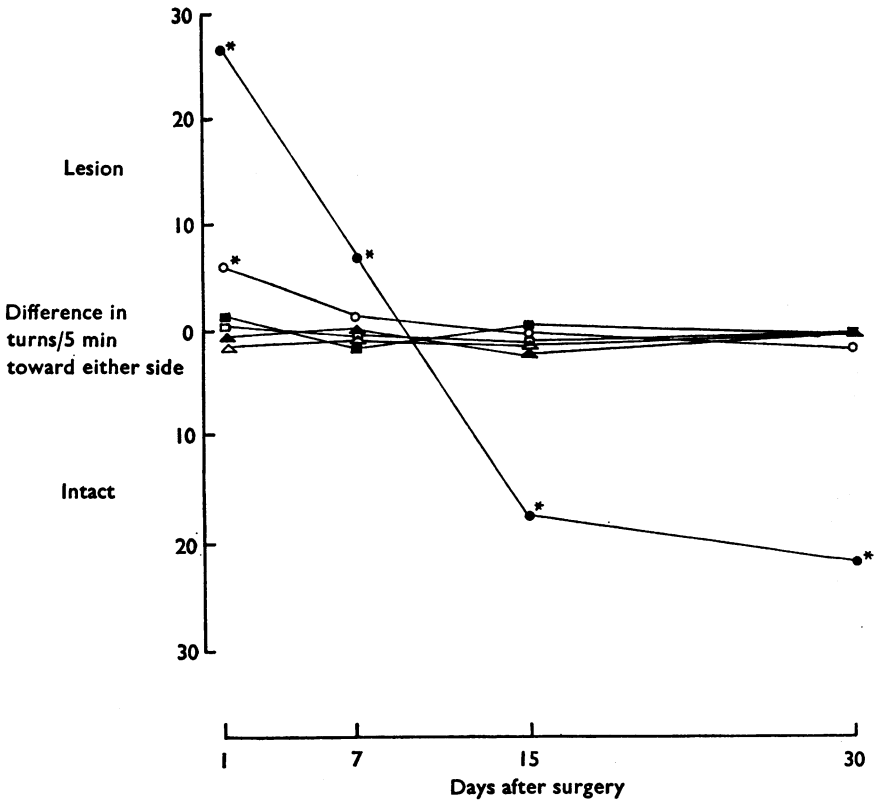


FIG. 2. Time-dependent changes in rotational behaviour following unilateral ablation of frontal cortex; different rats were used at each time point. A significant ($P<\cdot05$, $t$ test) difference between ipsilateral and contralateral turns is indicated by an asterisk. Symbols as in Figure 1.

surgery, drug condition during testing and past drug experience. At one day after surgery, rats with frontal cortical lesions rotated ipsilaterally; this occurred after saline and was potentiated by amphetamine. A significant directional tendency of these rats to rotate after saline administration did not occur at any other time point. In rats with frontal cortical lesions tested at all time points, amphetamine induced ipsilateral rotation at 3 and 7 days after surgery and slight but significant contralateral rotation at 30 days after surgery; there was no significant rotation in either direction at 15 days after surgery. In frontal rats tested at only one time point, amphetamine induced ipsilateral rotation 7 days after surgery and contralateral rotation at 15 and 30 days after surgery.

## Discussion

Rotational behaviour in rats with unilateral lesions of the nigro-striatal system has been attributed to an imbalance in the striatal dopamine activity of the two sides of the brain (Ungerstedt, 1971b, 1971c). A higher level of dopamine receptor activity in the striatum of one side elicits rotation to the other side (Ungerstedt, 1971c). Amphetamine, presumably by releasing dopamine (Ungerstedt, 1971b), stimulates the intact striatum and induces ipsilateral rotation (Ungerstedt, 1971b; Christie &

Crow, 1971). Amphetamine-induced ipsilateral rotation continues to occur even several months after a unilateral nigro-striatal lesion (Ungerstedt, 1971b). Drugs such as L-DOPA and apomorphine presumably stimulate dopaminergic receptors directly and induce contralateral rotation (Ungerstedt, 1971c); this latter effect occurs and increases as a function of time after surgery and has been attributed to time-dependent supersensitivity of denervated dopaminergic receptors in a striatum from which nigral input has been removed. Since amphetamine apparently acts predominantly on a striatum with intact nigral input, the intensity as well as the direction of rotation do not vary as a function of supersensitivity of the denervated striatum.

Rats with unilateral lesions of the frontal cortex also exhibited spontaneous and amphetamine-induced rotatory behaviour. Ipsilateral spontaneous rotation was transient, lasting only 1–3 days; recovery also occurs, though somewhat more slowly, following unilateral nigral lesions (Ungerstedt, 1971b, 1971c). Amphetamine potentiated and induced ipsilateral rotation in rats with frontal cortical lesions 1 and 3–7 days after surgery, respectively. This finding is also similar to that reported to occur in rats with substantia nigra lesions (Ungerstedt, 1971b; Christie & Crow, 1971). However, in contrast to the persistent effect of amphetamine in rats with substantia nigra lesions, amphetamine-induced ipsilateral rotation eventually disappeared in rats with frontal cortical lesions. The latter was followed by the appearance of amphetamine-induced contralateral rotation. Although there is no evidence for a specificially dopaminergic pathway between frontal cortex and the striatum, the present data do suggest that such a pathway (Knook, 1965), if not dopaminergic, at least modulates dopaminergic striatal functions. This modulation might be multi-synaptic and involve dopaminergic striatal interneurones converging on the same general pool of synapses innervated by ascending nigral projections. The spontaneous ipsilateral rotation of rats with unilateral frontal cortical lesions indicates a decrease in dopaminergic function of the ipsilateral striatum. Initially, amphetamine presumably potentiates the imbalance by predominantly stimulating the intact striatum. The disappearance of spontaneous rotation as well as the emergence of amphetamine-induced contralateral rotation both suggest that the ipsilateral striatum, as a result of a partial denervation, becomes supersensitive to remaining nigral input. Amphetamine-induced contralateral rotation in rats with unilateral nigral lesions would be less likely (Ungerstedt, 1971b) because the major striatal input had been removed and supersensitivity to the remaining cortical input would be insufficient to overcome stimulation of the intact striatum.

The rats treated only once with amphetamine were included so that time-dependent changes in drug sensitivity could be observed without possibly being confounded by prior drug administration. The same kinds of changes occurred in rats tested repeatedly with amphetamine and in rats tested only once. However, the changes seem to have occurred more rapidly in the latter case. Rats tested repeatedly showed amphetamine-induced contralateral rotation only at 30 days after surgery whereas rats tested only once showed this effect 15 days after surgery. Perhaps multiple administrations of amphetamine produced enough stimulation (i.e. by release of dopamine from intact nigral input) of the partially denervated striatum to slow the time-course of the developing supersensitivity.

This work was supported by NIMH grant 1 RO1 MH 21156-01 and Research Scientist Development Award 1 KO2 MH 70082-01 to S.D.G.

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(*Received October* 17, 1972)