## Differences in circling responses following electrolytic and 6-hydroxydopamine lesions of the nigro-striatal pathway

B. COSTALL, C.D. MARSDEN, R.J. NAYLOR & C.J. PYCOCK*

*University Department of Neurology, King's College Hospital and Institute of Psychiatry, London SE5 and Department of Pharmacology, University of Bradford*

After injection of 6-hydroxydopamine into one substantia nigra to destroy the nigrostriatal dopaminergic neurones, rats circle towards the side of the lesion when amphetamine is administered systemically (due to release of dopamine from the opposite intact nigrostriatal pathway), and away from the side of the lesion when given apomorphine (due to preferential stimulation of presumed supra-sensitive dopamine receptors in the denervated striatum) (Ungerstedt, 1971). However, if an electrolytic lesion is placed in one nigrostriatal pathway, rats circle towards the side of the lesion when either apomorphine or amphetamine is administered (Costall & Naylor, 1975). We have therefore examined the biochemical and behavioural differences between a unilateral 6-hydroxydopamine lesion and an electrolesion of the nigrostriatal pathway. The results are summarized in the Table.

Unilateral injection of 6-hydroxydopamine (8 $\mu$g in 4 $\mu$l) just anterior to substantia nigra (A 30, V−2.7, L±2.0; De Groot, 1959), or into the medial forebrain bundle at the level of the lateral hypothalamus (A 4.6, V − 2.7, L ± 1.9), caused a profound reduction in ipsilateral striatal dopamine concentration. The nigral injection had no effect on cortical noradrenaline or striatal 5-hydroxytryptamine. The medial forebrain bundle lesion but not the nigral lesion caused a fall in cortical noradrenaline. Both lesions resulted in contraversive rotation to s.c. apomorphine and ipsiversive rotation to i.p. amphetamine. The medial forebrain bundle lesion caused enhanced contralateral postural deviation and circling to dopamine (50 to 100 $\mu$g in 1 $\mu$l) injected into the denervated striatum.

Unilateral electrolesions of substantia nigra (A 2.2, V − 1.7, L ± 2.0) or medial forebrain bundle at the level of the lateral hypothalamus (A 4.6, V − 2.7, L ± 1.9) caused changes in forebrain monoamine concentrations, including a considerable drop in ipsilateral striatal dopamine. But these electrolesions caused ipsiversive rotation to both s.c. apomorphine and i.p. amphetamine (the threshold dose of apomorphine required being

**Table 1** Comparison of effects of unilateral 6-hydroxydopamine and electrolytic lesions on forebrain monoamines and drug-induced circling behaviour

| | *6-hydroxydopamine* | | *Electrolesion* | |
|---|---|---|---|---|
| | *Substantia nigra* | *Medial forebrain bundle* | *Substantia nigra* | *Medial forebrain bundle* |
| | *Forebrain monoamine concentrations** | | | |
| Striatal dopamine | 29%[c] | 18%[c] | 25%[c] | 57%[a] |
| Cortical noradrenaline | 83% | 63%[b] | 103% | 67%[a] |
| Striatal 5-hydroxytryptamine | 91% | 91% | 90% | 83% |
| | *Effect of systemic administration of drugs†* | | | |
| Amphetamine | I 0.63 | I 0.63 | I 1.25 | I 1.25 |
| Apomorphine | C 0.03 | C 0.015 | I 0.125 | I 0.125 |
| | *Effects of intrastriatal dopamine‡* | | | |
| | — | Marked contraversive posture or circling | Nil | — |

* Forebrain monoamine concentrations ipsilateral to the side of the lesion are expressed as a per cent of values in the opposite intact side.

† The direction of circling behaviour is indicated by I = towards the side of the lesion, and C = away from the side of the lesion. The threshold dose of drug (in mg/kg, i.p. or s.c.) required to produce such circling is also shown.

‡ Direct intrastriatal injection of 100 $\mu$g-of dopamine into one intact striatum produced periodic contralateral postural asymmetry but no circling. The effect of injection of dopamine (50-100 $\mu$g) into the denervated striatum is shown.

Superscripts indicate significance (Student's *t* test of paired samples) a = $P < 0.01$, b = $P < 0.005$, c = $P < 0.001$.

more than four-fold greater than that required to cause contraversive rotation after 6-hydroxydopamine lesions). The substantia nigra electrolesion abolished the effects of intrastriatal dopamine.

If an electrolesion in substantia nigra was followed by a 6-hydroxydopamine injection into the medial forebrain bundle, unilateral striatal dopamine fell to 33% of normal. Such animals rotated only ipsiversively to both s.c. apomorphine and i.p. amphetamine.

An electrolesion in substantia nigra (or medial forebrain bundle) appears to abolish the effect of s.c. apomorphine or intrastriatal dopamine on the denervated striatum. We conclude that such electrolesions destroy not only the ascending nigrostriatal dopaminergic pathway, but also a second neuronal system, perhaps a non-dopaminergic nigrostriatal tract or a strio-pallidal efferent pathway, required for expression of rotational behaviour resulting from stimulation of dopaminergic receptors in the denervated striatum.

Drs B.C. and R.J.N. acknowledge support from the Medical Research Council. C.P. is a Fellow of the Parkinson's Disease Society.

**References**

COSTALL, B. & NAYLOR, R.J. (1975). Actions of dopaminergic agonists on motor function. *Adv. Neurol.*, 9, 285-297. Ed. D.B. Calne, T.N. Chase & A. Barbeau, Raven Press, New York.

DE GROOT, J. (1959). The Rat Brain in Stereotaxic Co-ordinates. *Verh. K. Ned. Akad. Wet.*, **52**, p. 14.

UNDERSTEDT, U. (1971). Postsynaptic supersensitivity after 6-hydroxydopamine induced degeneration of the nigro-striatal dopamine system. *Acta physiol. scand.*, **82**, *Suppl.*, **367**, 69-93.

## The role of dopamine in rotational behaviour produced by unilateral lesions of the locus coeruleus

I. DONALDSON*, ANNETTE DOLPHIN, P. JENNER, C.D. MARSDEN & C. PYCOCK

*Dept. of Neurology, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF*

Rats with unilateral electrolytic lesions of the locus coeruleus rotate contraversive to the side of the lesion when given apomorphine hydrochloride (1 mg/kg i.p.) or dexamphetamine sulphate (5 mg/kg i.p.). This turning is transient and persists for less than 2 months. It is accompanied by a rise in the dopamine content of the ipsilateral striatum which is also transient and has a similar time course to the turning (Marsden & Pycock, 1974; Pycock, Donaldson & Marsden, 1975). Further experiments suggest that it is due to asymmetrical stimulation of the striatal dopamine receptors.

The turning induced in such animals by dexamphetamine is not modified by pretreatment with alpha (phenoxybenzamine 20 mg/kg i.p. 90 min before) or beta (propanolol 5 mg/kg i.p. immediately before) adrenoceptor blockers. However, turning to both dexamphetamine and apomorphine is completely abolished by pretreatment with the dopamine receptor blocker pimozide (0.25 mg/kg i.p. 4 h before). Similarly the adrenoceptor stimulant clonidine (0.05-0.5 mg/kg i.p.) does not produce rotation whereas the dopamine receptor stimulant piribedil (100 mg/kg i.p.) does.

Rotation produced by a locus coeruleus lesion is abolished by a unilateral electrolytic lesion of the substantia nigra on the same side. The resultant turning is the same as that normally produced by the substantia nigra lesion alone.

Intrastriatal injections in rats with unilateral locus coeruleus lesions show that the striatum on the side of the locus lesion is more sensitive to apomorphine than the opposite striatum. The dose of apomorphine required to produce rotation when injected intrastriatally on the side of the lesion was only $22 \pm 6$ micrograms while $61 \pm 9$ micrograms was required to produce the same effect when injected into the opposite striatum.

These results are consistent with the suggestion that the drug induced turning behaviour due to a unilateral locus coeruleus lesion in the rat is mediated via the ipsilateral striatal dopamine receptors. Their behaviour may be altered by the locus lesion which may have a facilitatory effect on transmission in the ipsilateral nigrostriatal pathway.

**References**

MARSDEN, C.D. & PYCOCK, C. (1975). Transient contraversive turning produced by unilateral lesions in the region of the locus coeruleus. *J. Physiol.*, **244**, 85-86.

PYCOCK, C., DONALDSON, I. MacG. & MARSDEN, C.D. (1975). Circling behaviour produced by unilateral lesions in the region of the locus coeruleus in rats. *Brain Res.* (in press).