Circling behaviour produced by asymmetric medial raphé nuclei lesions in rats

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When amphetamine or apomorphine are administered to rats with asymmetric electrolesions of the midbrain medial raphé nuclei (MRN), the animals turn in tight circles away from the side of the lesion (Costall & Naylor, 1974a). This circling behaviour persists for at least 56 days after surgery.

When amphetamine or apomorphine are administered to rats with unilateral electrolesions of the locus coeruleus (LC), the animals turn in tight circles away from the side of the lesion (Marsden & Pycock, 1974; Pycock, Donaldson & Marsden, 1975). This circling is transient, usually disappearing within about 30 days of surgery.

The close proximity of the dorsal noradrenaline bundle (which contains ascending fibres from the LC) to the MRN in the midbrain raises the question as to whether the asymmetric MRN electrolesions produce circling by damage to ascending noradrenaline pathways. The direction of drug-induced circling after unilateral electrolesions of MRN or LC is the same, although the duration of this behaviour differs. In careful histological studies, Costall & Naylor (1974a) concluded that contralateral circling produced by asymmetric midbrain lesions only occurred when the MRN was damaged, and not when the lesion only involved the lateral mesencephalic reticular formation containing the ascending noradrenaline pathways. However, subsequent work (Donaldson, Marsden & Pycock, unpublished data) has shown that an electrolesion confined to the region of the ventral noradrenaline bundle causes transient contraversive circling to apomorphine and (+)-amphetamine. No biochemical data were available to confirm the selectivity of the MRN lesions in Costall & Naylor's (1974a) original study. We have, therefore, repeated the experiments with subsequent histological examination of the site of the MRN electrolesions, and biochemical estimation of monoamines in forebrain structures.

Stereotaxic surgery was carried out under chloral hydrate anaesthesia (300 mg kg^{-1}). Electrolesions were placed in the region of the medial raphé nucleus (A 0·3, V −2·6, L ±0·3; König & Klippel, 1963) in male Sprague Dawley rats (275–325 g), using a Kopf stereotaxic instrument and stainless steel electrodes (0·65 mm in diameter), insulated except at the tip, with currents of 0·5 mA for 10 s 12 to 24 days after surgery animals were tested for circling behaviour to apomorphine (0·015–0·5 mg kg^{-1}, s.c.) or (+)-amphetamine (0·63–5 mg kg^{-1}, i.p.). Net turns min^{-1} were recorded. 12 rats which exhibited good circling responses were then selected for intrastriatal injection studies. Stainless steel guide cannulae (0·65 mm in diameter) were chronically implanted such that an injection unit (0·3 mm in diameter, stainless steel) extending 1·5 mm below the guide tip deposited 1 μl dopamine or solvent at the centre of the caudate-putamen (A 8·0, V +1·5, L ±3·0; De Groot, 1959). Upon completion of the studies the brains of randomly selected rats were subjected to the biochemical techniques described by Costall, Fortune & others (1975).

Dopamine hydrochloride (Koch Light) was prepared for intrastriatal injection in nitrogen bubbled distilled water and the pH adjusted to 7·4 with sodium bicarbonate immediately before use. (+)-Amphetamine sulphate (Sigma) was prepared in distilled water and apomorphine hydrochloride (Macfarlan Smith) in distilled water containing 0·1% sodium metabisulphite.

Rats with asymmetric MRN lesions spontaneously circled away from the side of the lesion, particularly in the first 3 post-operative days but persistently thereafter. This contralateral circling was markedly enhanced by both apomorphine and (+)-amphetamine in a dose-dependent manner (Fig. 1).

The unilateral injection of dopamine (100 μg in 1 μl over 5 s) into one striatum of normal rats caused deviation of the head and neck to the opposite side, with body rotation in the same direction when the animal was disturbed (50 μg was without effect). After unilateral MRN lesions, the response to intrastriatal dopamine was similar to that of normal animals.

The effects of asymmetric MRN lesions on forebrain monoamine concentrations are summarized in Table 1. 5-Hydroxytryptamine concentrations on the side of the lesion in cerebral cortex, limbic area and corpus striatum were reduced by 27, 25 and 22% respectively compared with the normal side. Dopamine in the meso-

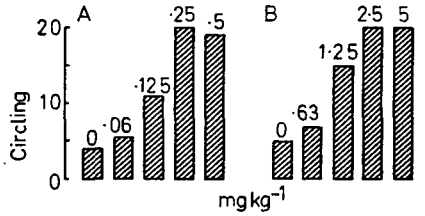

FIG. 1. The enhancement of contraversive circling behaviour by A-apomorphine and B-(+)-amphetamine in rats 12 to 24 days after asymmetric lesions of the MRN. Circling was measured in rev min^{-1} every 15 to 30 min throughout the action of a drug and is expressed as the maximum attained. Each value is the mean of responses from 8 to 10 animals. Standard errors are all less than 14% of the means.

Table 1. *Effect of asymmetric MRN lesions on forebrain monoamine concentrations (expressed as ng g^{-1} wet weight of tissue ± s.e.m.).*

	5-HT		Dopamine		Noradrenaline	
	Control side	Lesioned side	Control side	Lesioned side	Control side	Lesioned side
Cerebral cortex	353 ± 28	259 ± 18**	—	—	301 ± 22	300 ± 18
Mesolimbic area	540 ± 53	406 ± 41*	1060 ± 200	840 ± 150	450 ± 35	417 ± 33
Corpus striatum	715 ± 40	559 ± 47**	3020 ± 380	2650 ± 320	—	—

Significance (Student's *t*-test of paired samples): * $P < 0.05$; ** $P < 0.01$.

limbic area and corpus striatum and noradrenaline in the cerebral cortex and mesolimbic area, were not altered significantly.

The asymmetric MRN electrolesions, which caused intense and persistent spontaneous contraversive circling behaviour that was markedly enhanced by apomorphine and (+)-amphetamine, were associated with a selective depletion of forebrain 5-hydroxytryptamine. No biochemical evidence for damage to either the nigrostriatal dopamine system or the ascending noradrenaline pathways was found. Cortical, mesolimbic and striatal 5-hydroxytryptamine were reduced on the side of the lesion to approximately the same degree, in agreement with previous findings (Costall & others, 1975). Thus, circling behaviour after asymmetric MRN lesions appears to be due to selective damage to ascending 5-hydroxytryptamine pathways.

The induction of spontaneous and drug induced circling away from the side of the MRN lesion suggests a preferential stimulation of the ipsilateral striatum by a direct stimulation of striatal dopamine receptors (apomorphine) or by release of dopamine from the nigrostriatal system (amphetamine). However, we found no enhanced sensitivity to dopamine applied directly to the striatum on the side of the MRN lesion. This suggests that the striatal dopamine mechanism, activated by dopamine receptor stimulation to cause circling, is not rendered unduly over-active by the MRN lesion. In support of this conclusion is the observation that the threshold dose of apomorphine required to potentiate contraversive circling after MRN lesions was 0·125 mg kg^{-1}, whereas in similar studies we have found that as little as 0·015 mg kg^{-1} of apomorphine will cause contraversive circling in animals with a unilateral 6-hydroxydopamine lesion of the nigrostriatal dopamine pathways (Costall, Marsden & others, unpublished data).

It is also difficult to reconcile our findings with results from intrastriatal injection studies where 5-HT injected into the caudate-putamen of rat has been shown to evoke a contralateral circling (Costall & Naylor, 1974b) and facilitate contralateral motor effects in the cat (Cools, 1974). Depletion of striatal 5-HT by an asymmetric MRN lesion clearly produces effects opposite to those which may be expected from studies on the responses which follow 5-HT manipulation within the striatum.

We therefore have no convincing explanation as to why an asymmetric MRN lesion causes contraversive turning. Certainly, it does not seem to depend on damage to other monoamine pathways. It appears to be due to preferential activity of the ipsilateral striatal complex, but none could be shown to direct intrastriatal application of dopamine.

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