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Differential rotational behaviour after unilateral 5,7-dihydroxytryptamine induced lesions of the dorsal raphé nucleus

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Rats with unilateral lesions of the dopamine containing neurones, of the ascending nigrostriatal pathway exhibit behavioural asymmetry (Andén, Dahlström, Fuxe & Larsson, 1966) and a functional imbalance in locomotor control expressed as a characteristic form of 'rotational' behaviour when administered drugs which facilitate dopaminergic neurotransmission (Ungerstedt, 1971).

However, the relationship between dopamine dependent rotational behaviour and the possible involvement of other neurotransmitter systems is far from clear since lesions outside the nigrostriatal pathway induce similar behavioural phenomena (Glick, Jerussi & Fleischer, 1976). Recent evidence suggests that 5-HT afferents from the dorsal (DRN) and medial (MRN) raphe nuclei modulate nigrostriatal function (Dray, Conye, Oakley & Tanner, 1976; Haigler & Aghajanian, 1974; Pasquier, Kemper, Forbes & Morgane, 1977). The aim of the present study was to assess the effect of unilateral dorsal raphé lesions on nigrostriatal function as might be revealed by rotational behaviour.

Adult male rats of the Alderley Park SPF strain (180–200 gm) were pretreated with pargyline HCl (50 mg/kg i.p.) one hour before the injection of 5,7-dihydroxytryptamine (5,7-DHT), dissolved in 2 μl of 0.9% saline (8 μg base/μl). The neurotoxin was injected under halothane anaesthesia over a period of 5 min through the cerebellum at an angle of 47° to the vertical plane in a Kopf stereotaxic instrument (DRN coordinates: 5.4 caudal to lambda, 1.0 lateral to the midline and 9.4 ventral to the surface of the skull, according to the Skinner stereotaxic atlas). Sham operated controls received 2 μl of saline with and without ascorbate antioxidant (0.2 mg/ml).

Unilateral DRN lesions induced transient spontaneous tight ipsiversive rotation following surgery which had disappeared by the second post-operative day. On the third post-operative day all rats were tested for rotational behaviour by challenging with either apomorphine or 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeODMT); rotational behaviour being assessed in automated rotometers (Barber, Blackburn & Greenwood, 1973). When challenged with apomorphine, lesioned animals displayed a dose-related ipsilateral rotational response (0.3 turns/min at 0.5 mg/kg s.c. to 4.5 turns/min at a dose of 1.0 mg/kg s.c.). In contrast, administration of 5-MeODMT to these animals produced a dose related contraversive rotational response (1.4 turns/min at a dose of 1.0 mg/kg s.c. to 4.2 turns/min at a dose of 7.5 mg/kg s.c.). All drug induced rotations were completely blocked by haloperidol (0.3 mg/kg i.p.), and significantly reduced by methysergide (10 mg/kg i.p.).

Following rotational studies, groups of lesioned animals were sacrificed and regional neurochemical assays revealed a significant reduction in striatal, anterior cortical and nigral 5-HT concentration on the lesioned side (67%, $P < 0.001$; 34%, $P < 0.005$ and 45%, $P < 0.001$ respectively). A significant and selective decrease in the uptake of [^{3}H]-5-HT was also observed in cortical and striatal tissue on the lesioned side.

Our observations are consistent with other studies in which L-5-hydroxytryptophan evoked contralateral rotation in rats with unilateral 5,7-DHT induced lesions of the DRN-forebrain tract at the level of the medial forebrain bundle (Jacobs, Simon, Ruimy & Trulson, 1977; Azmitia & Segal, 1978). The available neurochemical data suggests that the main effect of unilateral lesions of the DRN is to cause a loss of forebrain 5-HT possibly resulting in supersensitivity on the denervated side; an effect revealed by contralateral rotation in response to 5-HT agonists.

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Dopamine mediated circling behaviour is modulated by lesions of the ventromedial nucleus of the thalamus

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The destination of basal ganglia efferent pathways responsible for apomorphine-induced circling in rats with striatal dopamine receptor imbalance are unknown. Output pathways from the zona reticulata of the substantia nigra are involved, but not the major outflow to the superior colliculus (Jenner, Leigh, Marsden & Reavill, 1979). Other structures receiving fibres from the substantia nigra include the ventromedial (VM) and parafascicular (PF) nuclei of the thalamus (Herkenham, 1979). We now report the effect of lesions of these bodies on circling behaviour in male Wistar rats.

Unilateral electrolytic lesions of VM (A 4.8; L 1.2; V − 1.3) or PF (A 3.4; L 1.0; V − 0.8) (De Groot, 1959) 15 days previously did not cause spontaneous turning. Apomorphine hydrochloride (0.5 mg/kg s.c. 15 min previously) or amphetamine sulphate (3 mg/kg i.p. 30 min previously) caused slow wide ipsiversive turning (<2 turns/min) in both VM and PF lesioned animals.

Animals receiving unilateral 6-hydroxydopamine (6-OHDA; 8 μg/3 μl 0.9% saline) lesions of the medial forebrain bundle (MFB) at the level of the left lateral hypothalamus (A 4.6; L 1.9; V − 3.0) 9 days previously showed tight contraversive circling to apomorphine (18.8 ± 3.9 turns/min) and ipsiversive circling to amphetamine (10.5 ± 0.7 turns/min). Subsequent electrolytic lesioning of VM on the side of the 6-OHDA lesion caused a 60% reduction in apomorphine (control animals 18.8 ± 3.9 turns per min; VM lesion 7.5 ± 1.8 turns/min; $P < 0.05$). Amphetamine-induced circling was unaltered (control animals 10.5 ± 0.7 turns/min; VM lesion 8.5 ± 0.4 turns/min; $P > 0.05$). Further, electrolytic lesioning of VM on the opposite side to the initial 6-OHDA lesion caused a 86% reduction in amphetamine-induced circling (control animals 7.1 ± 2.4 turns/min; VM lesion 1.0 ± 0.5 turns/min; $P < 0.5$) while apomorphine-induced circling was unaltered (control animals 11.4 ± 2.7 turns/min; VM lesion 11.0 ± 1.6 turns/min; $P > 0.05$).

Circling to apomorphine or amphetamine in animals with an unilateral 6-OHDA MFB lesion was unaltered by a subsequent unilateral PF lesion irrespective of side.

This evidence would suggest an important role of VM in the efferent pathway controlling circling behaviour. However, subsequent bilateral lesioning of VM or PF in animals with a unilateral MFB lesion failed to inhibit circling in response to apomorphine or amphetamine. This may indicate that VM modulates striatal induced circling rather than acting as a critical basal ganglia outflow station mediating the turning behaviour.

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