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The involvement of dopaminergic systems with the stereotyped behaviour patterns induced by methylphenidate

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The electrolytic brain lesion technique was used to investigate the role of dopamine-containing areas and pathways in the rat for the mediation of methylphenidate stereotypy. Ablation of the dopaminergic pathways to the extrapyramidal areas at the level of the lateral hypothalamus or substantia nigra was without effect suggesting a postsynaptic site of action in the extrapyramidal nuclei. This site was shown to be the paleo- and not the neostriatum. Deafferentation of the mesolimbic nuclei abolished the weaker components of stereotypy in the acute phase. This effect was generally reflected by ablation of the tuberculum olfactorium but not by nucleus accumbens septi or nucleus interstitialis stria terminalis lesions. The action in the mesolimbic areas may, therefore, involve presynaptic mechanisms. Lesion of the nucleus amygdaloideus centralis abolished the intense components of stereotypy. The greater importance of extrapyramidal function for the action of methylphenidate would indicate a possible value for this agent in the treatment of Parkinson's disease.

All current drugs used for the treatment of parkinsonism are either able to induce a stereotyped behaviour or enhance that induced by amphetamine (Costall, Naylor & Wright, 1972). The relation between stereotypy and activity against parkinsonism can be understood since stereotypy is considered to result from a stimulation of the nigrostriatal dopaminergic system (Fog, 1972) whilst parkinsonism is associated with its degeneration (Hornykiewicz, 1966). However, the mechanism by which a drug induces stereotyped behaviour is of critical importance since a drug which mimics nigrostriatal stimulation by an action at presynaptic sites may only be of value in disease states characterized by incomplete degeneration of the nigrostriatal pathway, whereas a drug acting directly upon the striatal dopamine receptors may have a wider application to the treatment of parkinsonism.

The present studies were, therefore, designed to investigate the sites and mechanisms involved in the mediation of the stereotyped behaviour patterns induced by methylphenidate by application of the brain lesion technique to directly ablate or deafferentate dopamine-containing areas in the rat brain.

MATERIALS AND METHODS

Male Sprague-Dawley (Bradford Strain) rats, weighing 250–300 g at the time of operation or at the beginning of an experiment, were housed and stereotypy assessed according to the method of Costall & Naylor (1973a). Briefly, the intensity of stereotypy was assessed at frequent intervals following methylphenidate administration. To reduce the subjectivity of assessments, Latin square designs were employed

Table 1. *Stereotaxic coordinates and lesion parameters for the induction of electrolytic brain lesions to disrupt dopaminergic pathways or areas in the rat brain.*

Lesion location	Stereotaxic Coordinates* Ant	Lat	Vert**	Lesion Parameters mA	s
Ascending dopaminergic pathways to extrapyramidal and mesolimbic areas in the lateral hypothalamus	4·6	1·7	−2·7 (−2·3)	0·5	10
Ascending dopaminergic pathways to mesolimbic areas in the rostral hypothalamus	6·6	2·3	−1·0 (−0·4)	0·5	10
Caudate-putamen complex	9·0	2·5	+1·0 (+3·5)	2·0	15
	8·0	3·0	+1·5 (+3·5)		
	7·0	3·0	+2·5 (+3·5)		
Globus pallidus	7·0	3·0	0·0 (+1·0)	2·0	10
Substantia nigra	2·2	2·0	−1·7 (−1·2)	0·5	10
Nucleus amygdaloideus centralis	5·8	4·3	−1·7 (−1·25)	0·5	10
Nucleus interstitialis stria terminalis	7·0	1·5	+0·5 (+1·0)	0·5	10
Nucleus accumbens septi	9·4	1·6	−0·15 (+0·85)	2·0	15
Tuberculum olfactorium	9·0	2·5	−2·6 (−2·2)	1·0	10
	10·0	2·0	−1·9 (−1·3)		

* Stereotaxic coordinates selected with the aid of the atlas of De Groot (1959) and the studies of Ungerstedt (1971). ** Vertical coordinates for sham-operated rats are in parentheses.

to give a minimum of 8 determinations at each dose level of drug. Observations were made on the 2nd, 4th and 6th post-operative days*.

Lesions were induced bilaterally in the dopamine-containing areas and pathways shown in Table 1 using the electrolytic coagulation technique and the coordinates indicated. The detailed technique and the localization and extent of the lesions have been reported previously (Costall & Naylor, 1973a).

Methylphenidate hydrochloride (Ciba-Geigy Ltd.) was dissolved in normal saline and administered by the intraperitoneal route in a volume of 1 ml kg^{-1}.

RESULTS

Methylphenidate, in doses greater than 5 mg kg^{-1}, was found to induce a stereotyped behaviour of dose-dependent intensity in the rat. The stereotypy was characterized by sniffing and repetitive head movements at lower doses and by continuous biting, gnawing or licking at the higher doses. The maximum stereotypy score was 0, 1 $\pm$ 0·1, 2 $\pm$ 0·3, 4, 4, at 0, 10, 20, 30, 40 mg kg^{-1} drug respectively.

Lesions placed in the lateral hypothalamus to interrupt the ascending dopaminergic pathways from the mesencephalon to the subcortical extrapyramidal and mesolimbic nuclei were not found to modify methylphenidate stereotypy on any day of testing. Similarly, lesion of the substantia nigra, the origin of the ascending nigrostriatal dopaminergic pathway, did not modify the stereotyped behaviour patterns. Lesions of the caudate-putamen complex (neostriatum) failed to modify stereotypy but globus pallidus (paleostriatal) lesions abolished or markedly reduced all components of the methylphenidate effect on each day of testing (Table 2).

Destruction of the dopaminergic pathways to the mesolimbic brain areas (rostral hypothalamus) caused abolition of the weaker components of stereotypy, sniffing and

* Scoring system used for estimation of the intensity of stereotyped behaviour: appearance same as saline treated rats, 0; discontinuous sniffing and locomotor activity, 1; continuous sniffing and small head movements, periodic locomotor activity, 2; continuous sniffing, discontinuous biting or chewing, brief periods of locomotor activity, 3; continuous gnawing, biting and licking, no locomotor activity, 4.

Table 2. *Effect of lesions placed to destroy dopamine-containing pathways and nuclei associated with the extrapyramidal, mesolimbic and amygdaloid brain areas upon the stereotyped behaviour patterns induced by methylphenidate.*

Brain region lesioned	Effect of methylphenidate, 30 mg kg^{-1} (as % controls) on postoperative days		
	2	4	6
None	100	100	100
Ascending dopaminergic pathways to extrapyramidal and mesolimbic areas in the lateral hypothalamus	100	100	100
Ascending dopaminergic pathways to mesolimbic areas in the rostral hypothalamus	75*	75*	100
Substantia nigra	100	100	100
Caudate-putamen complex	—	—	100
Globus pallidus	0	0	25
Tuberculum olfactorium	80*	100	100
Nucleus interstitialis stria terminalis	100	100	100
Nucleus accumbens septi	100	100	100
Nucleus amygdaloideus centralis	50**	50**	50**

* $P < 0{\cdot}05$. At all these values the weak intensity components of stereotyped behaviour were absent. ** $P < 0{\cdot}001$.

The tabulated results do not significantly differ ($P > 0{\cdot}05$) from those obtained using 20 mg kg^{-1} methylphenidate. The responses of sham-operated and normal animals were indistinguishable, therefore, values obtained from sham-operated animals were used for construction of the table. All lesions were induced on the same occasion excepting those in the caudate-putamen where a 7 day recovery period was allowed between the induction of lesions in the 2 hemispheres: observations were, therefore, carried out only on the 6th day following the 2nd lesion procedure.

repetitive head movements, on the 2nd and 4th post-operative days, and the intense gnawing, biting and licking responses were periodic in nature. However, by the 6th post-operative day the nature of the methylphenidate stereotypy was indistinguishable from that induced in control animals. The weaker components of stereotypy were similarly abolished in some animals with tuberculum olfactorium lesions on the 2nd post-operative day although the behaviour induced on the 4th and 6th days was indistinguishable from control responses. The intensity of methylphenidate stereotypy was not modified by lesion of the nucleus interstitialis stria terminalis or nucleus accumbens septi on any day of testing although onset of stereotypy was significantly more rapid in the latter animals ($P < 0{\cdot}001$) (Table 2). Lesion of the central nucleus of the amygdala abolished the intense components of methylphenidate stereotypy on all days of testing but the weaker components were unmodified (Table 2).

DISCUSSION

Lesions placed to destroy the ascending dopaminergic pathways supplying the subcortical extrapyramidal nuclei, either at the level of the lateral hypothalamus or substantia nigra, did not reduce the effectiveness of methylphenidate and this agent may, therefore, be acting at postsynaptic sites in the extrapyramidal nuclei. Of these nuclei, the neostriatum has been consistently implicated as a site for the action of stereotypic agents and drugs active against parkinsonism (Fog, 1972) but the present studies indicated the integrity of the paleo- rather than neostriatum to be important for the action of methylphenidate. Similar findings have been reported for apomorphine and ET495 (Costall & Naylor, 1973a, b) which produce favourable effects upon the symptoms of parkinsonism (Braham, Sarova-Pinhas & Goldhammer, 1970;

Cotzias, Papavasiliou & others, 1970; Castaigne, Laplane & Dordain, 1971; Düby, Cotzias & others, 1971; Strian, Micheler & Benkert, 1972; Vakil, Calne & others, 1972).

Although stereotypy has been considered by many workers purely in terms of extrapyramidal action, previous studies using apomorphine and ET495 have shown that mesolimbic and amygdaloid functions are also important for the initiation of their stereotyped responses (Costall & Naylor, 1973a, b). The present studies extend these observations to methylphenidate, since ablation of the mesolimbic innervation in the rostral hypothalamus was shown to reduce the weaker components of methylphenidate stereotypy during the acute stage (an effect possibly involving the tuberculum olfactorium since ablation of this mesolimbic area, but not of the nucleus accumbens septi or nucleus interstitialis stria terminalis, produced similar effects to lesions of the pathways) and lesions of the central amygdaloid nucleus abolished the intense gnawing, biting and licking components.

It is interesting that, whereas the 'striatal' effects of methylphenidate appear to be of a postsynaptic nature, its effects on mesolimbic areas may involve presynaptic mechanisms since deafferentation of the mesolimbic nuclei was equally or more effective than lesion of the areas themselves. However, the integrity of the extrapyramidal nucleus, the globus pallidus, would appear the more important for initiation of methylphenidate stereotypy and it is, therefore, suggested that methylphenidate may be of value in alleviating those symptoms of parkinsonism associated with extrapyramidal dopaminergic dysfunction.

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