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BACKWARD WALKING AND CIRCLING: BEHAVIOURAL RESPONSES INDUCED BY DRUG TREATMENTS WHICH CAUSE SIMULTANEOUS RELEASE OF CATECHOLAMINES AND 5-HYDROXYTRYPTAMINE

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1 The roles of catecholamine and 5-hydroxytryptamine (5-HT) release in mediating backward walking and circling were studied in rats.

2 These behaviours occurred in animals given 15 mg/kg intraperitoneally of (+)-amphetamine (which predominantly releases catecholamines) or either *p*-chloroamphetamine or fenfluramine (which predominantly release 5-HT). They also occurred when smaller doses of (+)-amphetamine (5 mg/kg) and either *p*-chloroamphetamine (2–5 mg/kg) or fenfluramine (5 mg/kg) were given together.

3 Characteristic dopamine-dependent behaviours (rearing, licking, gnawing) resulting from (+)-amphetamine injection were greatly reduced by *p*-chloroamphetamine or fenfluramine.

4 Characteristic 5-HT-dependent behaviours (wet dog shake, hind limb abduction) resulting from injection of either *p*-chloroamphetamine or fenfluramine were unaffected by (+)-amphetamine.

5 Fragmentary backward walking and circling resulting from levallorphan injection (50 mg/kg s.c.) were *decreased* by (+)-amphetamine at low dosage.

6 Results in general strengthen previous evidence that backward walking and circling are mediated by simultaneous dopamine and 5-HT release.

7 The possible relevance of the above findings to hallucinogenic activity, amphetamine psychosis, schizophrenia and abnormal movements due to L-DOPA treatment is discussed.

Introduction

Rats injected with (+)-amphetamine at doses up to 10 mg/kg intraperitoneally show a behavioural pattern consisting of increased locomotion, rearing and stereotyped responses such as sniffing, licking, gnawing and head bobbing. These behaviours are thought to be mediated principally by dopamine release (Hollister, Breese & Cooper, 1974). A strikingly different behavioural pattern follows treatment with similar doses of *p*-chloroamphetamine or fenfluramine, consisting of increased locomotion, tremor, head and body shakes ('wet-dog' shakes), rigidity, reciprocal forepaw treading, Straub tail, hind-limb abduction and lateral head-weaving and is thought to result from release of 5-hydroxytryptamine (5-HT) (Trulson & Jacobs, 1976). However, Taylor, Goudie, Mortimore & Wheeler (1974) found that either amphetamine or fenfluramine at higher dosage (15 to 30 mg/kg) provoked behavioural patterns of considerable similarity with prominent abnormal locomotor activity, i.e. backward walking and tight circling. These behaviours have also been described after giving high doses of *p*-chloroamphetamine (Scheel-Kruger, 1972; Growdon, 1977).

Large doses of (+)-amphetamine cause release of 5-HT as well as dopamine and noradrenaline (NA) (Fuxe & Ungerstedt, 1970). This may be involved in the abnormal locomotor behaviours as they are enhanced by L-tryptophan and decreased by the inhibitor of 5-HT synthesis *p*-chlorophenylalanine, by the 5-HT receptor blockers methergoline and cyproheptadine and by fluoxetine which inhibits uptake of drugs into 5-HT neurones (Lees, Fernando & Curzon, 1979). As the dopamine receptor blockers α-flupenthixol and pimozide (Curzon, Fernando & Lees, 1979) also prevented these behaviours, they may be mediated by concurrent release of dopamine and 5-HT. The same mechanism may be responsible for the abnormal locomotor behaviour induced by higher doses of *p*-chloroamphetamine and fenfluramine as these drugs not only release 5-HT but also have properties consistent with similar though less marked effects on catecholamines. Thus *p*-chloroamphetamine increases brain dopamine turnover (Costa, Naimzada & Revuelta, 1971) and elevates the concentration of *O*-methylated derivatives of dopamine and NA (Scheel-Kruger, 1972; Leonard, 1976) while fenflura-

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mine decreases brain NA and dopamine (Ziance, Sipes, Kinnard & Buckley, 1972) and decreases synaptosomal uptake of DA (Koyoumdjian, Belin, Bardakdjian & Gonnard, 1976).

The involvement of 5-HT changes in behaviour induced by amphetamine (Kelly, 1977) and that of catecholamine changes in behaviour induced by 5-HT (Heal, Green, Boullin & Graham-Smith, 1976; Jacobs, Wise & Taylor, 1975) have been extensively studied. However, there is a lack of direct evidence for a specific behavioural response of intact animals to the simultaneous release of 5-HT and catecholamines.

In this paper the roles of catecholamine and 5-HT release in mediating backward walking and circling have been further characterized by studying the effects of *p*-chloroamphetamine and fenfluramine on these responses to amphetamine. As levallorphan and some other partial opiate agonists have also been reported to induce the abnormal motor behaviour (Schneider, 1968), effects of levallorphan alone and given together with amphetamine and *p*-chloroamphetamine were also investigated.

Methods

Male Sprague-Dawley rats (Anglia Laboratory Animals, Alconbury, Cambridge) weighing 180 to 220 g were housed in a quiet room, three to a cage (335 mm × 215 mm × 180 mm high) under a 12 h light-dark (red light) (06 h 00 min to 18 h 00 min) schedule at 23 ± 3°C. The animals had free access to food (Grain Harvesters Rodent diet) and water.

The following drugs were used: (+)-amphetamine sulphate (Smith, Kline and French, Ltd.); (±)-*p*-chloroamphetamine HCl (Regis Ltd.); (±)-fenfluramine hydrochloride (Servier Laboratories); levallorphan tartrate (Roche). All drugs were dissolved in 0.9% w/v NaCl solution (saline) and injected as 2.5 ml/kg body wt. Drugs were given intraperitoneally except for levallorphan which was given subcutaneously. The following doses as drug bases were used: (+)-amphetamine, 2, 5, 10, 15, 25 mg/kg; *p*-chloroamphetamine, 2, 5, 10, 15, 25 mg/kg; fenfluramine, 5, 15, 25 mg/kg. As well as these injections of single drugs (+)-amphetamine and *p*-chloroamphetamine were given together at combinations of 2, 5 and 10 mg/kg doses of each drug. Also (+)-amphetamine, 5 mg/kg was given together with fenfluramine, 5 mg/kg. Levallorphan in doses of 15, 25 and 50 mg/kg was given alone and in combination with *p*-chloroamphetamine, 5 mg/kg and (+)-amphetamine; 1, 5 mg/kg.

Drugs were given either between 10 h 00 min and 12 h 00 min or at 15 h 00 min as it was noted in preliminary experiments that behavioural responses were consistently less marked between 13 h 00 min and 15 h 00 min. Three cages of rats were scored concurrently for 1 h after injection. In experiments on the effect of (+)-amphetamine, plus *p*-chloroamphetamine the three cages contained rats given (+)-amphetamine, *p*-chloroamphetamine and (+)-amphetamine plus *p*-chloroamphetamine. A similar scheme was

Table 1. Behavioural effects of high doses of (+)-amphetamine, *p*-chloroamphetamine and fenfluramine

	Behavioural scores					
				Dopamine-dependent behaviours		
	5-HT-dependent behaviours	*Backward walking*	*Circling pivoting*	*Rearing*	*Gnawing licking*	*Forward walking*
(+)-Amphetamine						
10 mg/kg	0	0.5 ± 0.2	0.5 ± 0.2	4.3 ± 0.6	6.7 ± 0.6	4.3 ± 0.6
15 mg/kg	5.1 ± 2.1	3.0 ± 1.0	2.5 ± 0.8	2.5 ± 0.7	4.5 ± 0.7	5.2 ± 1.5
25 mg/kg	8.7 ± 2.4	16.3 ± 1.7	8.2 ± 1.5	0	0	2.4 ± 0.9
p-Chloroamphetamine						
10 mg/kg	20.7 ± 2.8	0	0	0	0	6.3 ± 0.7
15 mg/kg	23.6 ± 2.6	1.0 ± 0.8	0.4 ± 0.4	0	0	7.0 ± 0.8
25 mg/kg	32.5 ± 3.1	3.0 ± 1.5	2.7 ± 1.2	0	0	5.8 ± 1.1
Fenfluramine						
10 mg/kg	9.8 ± 1.8	0	0	0	0	1.1 ± 0.7
15 mg/kg	10.3 ± 1.5	2.1 ± 1.2	0	0	0	2.1 ± 0.8
25 mg/kg	19.6 ± 1.7	11.6 ± 1.1	3.8 ± 0.9	0	0	2.8 ± 0.7

Behaviour was scored as described under 'Methods'. Each value was obtained using 6 cages of 3 rats and given as mean score/cage ± s.e. Max. possible score = 18 except for 5-HT-dependent behaviours. Here four separate scores for reciprocal forepaw treading, hind limb abduction, body shakes and Straub tail were obtained and summated. Max. possible score = 72.

used in the experiments on (+)-amphetamine plus fenfluramine and on (+)-amphetamine or *p*-chloroamphetamine plus levallorphan.

The components of the behaviours were scored in all or none fashion (Taylor *et al.*, 1974), the maximum possible score for any component therefore being 6 per rat or 18 per cage. The following were scored: *abnormal motor behaviours*-(tight circling, pivoting and backward walking); *dopamine-dependent behaviours*-rearing, gnawing and licking-(scores for the latter two behaviours were combined and averaged); *5-HT-dependent behaviours*—'wet dog shake', reciprocal forepaw treading, Straub tail, hind-limb abduction. Forward locomotion was increased by amphetamine and also by *p*-chloroamphetamine and was therefore scored but not classified as either dopamine or 5-HT-dependent. Head bobbing and lateral head weaving which are produced by amphetamine and 5-HT releasing drugs respectively were scored but the data obtained are not presented as these movements could not be clearly differentiated in rats given the drug combinations. Results are given ± s.e. and statistical analyses were made by the Mann-Whitney U test.

Results

Behavioural effects of amphetamine, p-chloroamphetamine and fenfluramine given singly at high dosage

Amphetamine (10, 15, 25, mg/kg). The characteristic dopamine-dependent rearing and gnawing were most marked in the rats given 10 mg/kg (+)-amphetamine and were absent in those given 25 mg/kg (Table 1). The animals given 10 or 15 mg/kg adopted a distinctive stooped posture with head bobbing and stood in one place for long periods. The characteristic 5-HT-dependent behaviours did not occur in rats given 10 mg/kg (+)-amphetamine but were apparent at 15 mg/kg and more prominent at 25 mg/kg, the animals showing body tremor, wet dog shakes, reciprocal forepaw treading and hind-limb abduction. Tight circling, pivoting and backward walking were present to a minimal extent at 10 mg/kg but became more apparent at the higher doses and were the most prominent behaviours at 25 mg/kg.

p-*Chloroamphetamine (10, 15, 25 mg/kg).* Within about 3 min of injection of any of these doses of *p*-chloroamphetamine the rats exhibited striking hind-limb abduction with a flattened posture and slithered on their abdomens when moving forward. At the higher doses, wet dog shakes became increasingly frequent and Straub tail, reciprocal forepaw treading and lateral head weaving were seen. Rearing and gnawing were absent and while forward walking with some circling around the perimeter of the cage was seen in rats given 10 mg/kg, the latter behaviour was easily distinguishable from the tight circling and pivoting of rats given high doses of amphetamine. This and also backward walking did however occur in rats given 15 or 25 mg/kg *p*-chloroamphetamine but much less markedly than in animals given the high doses of amphetamine.

Fenfluramine (10, 15, 25 mg/kg). Fenfluramine produced striking hind-limb abduction and occasional body shakes but the other 5-HT-dependent behaviours were absent. Rats given fenfluramine were ataxic and appeared drowsy for most of the observation period but intermittent and prominent backward walking and some pivoting occurred in animals given 25 mg/kg.

Table 2 Behavioural effects of (+)-amphetamine (5 mg/kg) together with *p*-chloroamphetamine (5 mg/kg)

	Bahavioural scores					
	5-HT-dependent behaviours	*Backward walking*	*Circling pivoting*	*Dopamine-dependent behaviours* *Rearing*	*Gnawing/licking*	*Forward walking*
(+)-Amphetamine (5 mg/kg)	0	0	0	15.2 ± 0.7	3.1 ± 0.9	6.2 ± 0.9
(+)-Amphetamine (5 mg/kg) plus *p*-chloroamphetamine (5 mg/kg)	17.2 ± 1.4	3.8 ± 1.0*	3.5 ± 1.0*	0.8 ± 0.2†	0†	8.2 ± 1.5
p-Chloroamphetamine (5 mg/kg)	20.8 ± 1.6	0	0	2.7 ± 1.1	0	7.8 ± 1.0

General methods as in Table 1. Significance of differences from rats given either drug singly: *$P < 0.01$. Significance of differences from rats given amphetamine only: †$P < 0.01$.

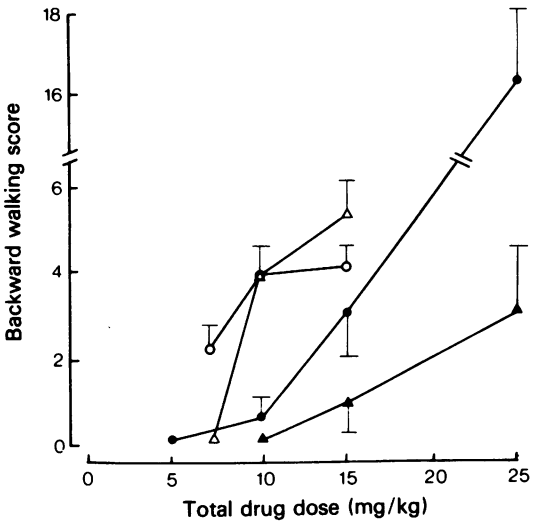

Figure 1 Backward walking after giving amphetamine and *p*-chloroamphetamine either singly or together. Amphetamine alone (●); *p*-chloroamphetamine alone (▲); amphetamine 5 mg/kg plus various doses of *p*-chloroamphetamine (○); *p*-chloroamphetamine 5 mg/kg plus various doses of amphetamine (△). Backward walking was scored as described in the Methods section. Each value was obtained using 6 cages of 3 rats and given as mean score/cage; vertical lines show s.e. Maximum possible score = 18. 'Total drug dose' indicates amphetamine plus *p*-chloroamphetamine. Essentially identical results were obtained when circling was scored instead of backward walking.

Behavioural effects of amphetamine (2, 5, 10 mg/kg) together with p-chloroamphetamine (2, 5, 10 mg/kg)

Rats given 5 mg/kg (+)-amphetamine showed dopamine-dependent behaviour (i.e. rearing etc.) but 5-HT-dependent behaviours and backward walking and circling were absent (Table 2). *p*-Chloroamphetamine 5 mg/kg caused marked 5-HT-dependent behaviour (i.e. hind-limb abduction) and also very occasional rearing but no backward walking or circling. However, when 5 mg/kg amphetamine was given together with 5 mg/kg *p*-chloroamphetamine a markedly different behavioural pattern resulted in which the dopamine-dependent behaviour was essentially absent but backward walking and circling occurred. 5-HT-dependent behaviour was comparable to that noted when 5 mg/kg *p*-chloroamphetamine was given alone. Backward walking and circling scores were not increased further by giving 10 mg/kg *p*-chloroamphetamine with 5 mg/kg amphetamine but were decreased when the *p*-chloroamphetamine dose was reduced to 2 mg/kg (Figure 1). Higher backward walking and circling scores were obtained with 10 mg/kg amphetamine plus 5 mg/kg *p*-chloroamphetamine but these behaviours were absent when the amphetamine dose was reduced to 2 mg/kg.

Behavioural effects of amphetamine (5 mg/kg) together with fenfluramine (5 mg/kg)

Administration of 5 mg/kg amphetamine plus 5 mg/kg fenfluramine produced a similar behavioural pattern to that seen after giving amphetamine plus *p*-chloroamphetamine (Table 3). This did not occur when the drugs were given singly at these doses.

Behavioural effects of levallorphan alone and together with (+)-amphetamine or p-chloroamphetamine

Levallorphan was given subcutaneously as preliminary experiments showed that behavioural effects were much greater than when it was injected intraperitoneally. Effects were maximal in the first 30 min

Table 3 Behavioural effects of (+)-amphetamine (5 mg/kg) together with fenfluramine (5 mg/kg)

	Behavioural scores					
	5-HT-dependent behaviours	*Backward walking*	*Circling/ pivoting*	*Dopamine-dependent behaviours Rearing*	*Gnawing/licking*	*Forward walking*
(+)-Amphetamine (5 mg/kg)	0	0	0	11.3 ± 0.3	5.6 ± 1.1	4.2 ± 0.7
(+)-Amphetamine (5 mg/kg) plus fenfluramine (5 mg/kg)	9.0 ± 1.0	4.8 ± 1.2*	2.7 ± 0.7*	2.2 ± 1.0†	0†	2.5 ± 0.8
Fenfluramine (5 mg/kg)	11.2 ± 1.7	0	0	0.3 ± 0.2	0	0.8 ± 0.2

General methods as in Table 1. Significance of differences from rats given either drug singly: *$P < 0.01$. Significance of differences from rats given amphetamine only: †$P < 0.01$.

after injection and had almost disappeared by 1 h. Levallorphan 15 mg/kg induced body rearing which differed from that seen in rats given amphetamine as the animals maintained upright posture for several minutes against the cage walls.

At higher doses (25, 50 mg/kg) postural instability and marked body and head rocking occurred. The rats also made occassional slow ataxic backward steps. Complete circling movements were not seen although the animals pivoted in semi-circles. Occasionally they stood on their hind limbs and exhibited violent clonic movements of their forepaws and some teeth grinding.

Levallorphan 15 mg/kg plus 5 mg/kg of either (+)-amphetamine or *p*-chloroamphetamine did not provoke backward walking or circling and the behaviours induced by the latter drugs were not modified by levallorphan. Doses as low as 1 mg/kg (+)-amphetamine, however, reduced the backward walking caused by 50 mg/kg levallorphan (Table 4).

Discussion

These experiments strengthen previous indications (Lees *et al.*, 1979) that the abnormal motor activity (backward walking and circling) induced by amphetamine at high dosage in rats is mediated by release of both dopamine and 5-HT. In agreement with Taylor *et al.* (1974) and Growdon (1977) this behaviour was also caused by high doses of *p*-chloroamphetamine or fenfluramine. As the effects of both of these substances on brain amine metabolism suggests that as well as releasing brain 5-HT they also have some ability to release catecholamines it is likely that the abnormal locomotor activity due to all three drugs involves the same mechanism. This receives further support from the effects of amphetamine given together with *p*-chloroamphetamine or fenfluramine. Thus, lower doses of amphetamine and either of the two predominantly 5-HT releasing drugs provoked abnormal motor activity when given together, but not when administered alone.

However, some doubt is cast on previous evidence that dopamine is involved in the above behaviours as this depends on the use of dopamine receptor blocking drugs (Curzon *et al.*, 1979; Lees *et al.*, 1979) and many of these drugs also block 5-HT receptors (Leysen, Niemegeers, Tollenaere & Laduron, 1978). Nevertheless, recent unpublished work (Curzon, Fernando & Lees) confirms the suggestion that dopamine release is necessary for backward walking and circling to occur as various dopamine blockers (haloperidol, pimozide, sulpiride and metoclopramide) prevented these behaviours at doses which had no effect on 5-HT-dependent behaviours.

Previous work indicates that 5-HT depresses amphetamine-provoked forward locomotor activity and also stereotypy (Mabry & Campbell, 1973; Weiner, Goetz, Westheimer & Klawans, 1973; Lees *et al.*, 1979). Similarly, in the present study, the 5-HT releasers *p*-chloroamphetamine and fenfluramine decreased rearing and gnawing due to amphetamine. However, as the abnormal locomotor activity increased when these 5-HT releasers were given with amphetamine, a differential role of 5-HT between this and the above behaviours is indicated.

Although dopamine receptor *blockers* are reported to decrease characteristic behavioural responses to 5-HT releasers (Heal *et al.* 1976), these responses were not increased by amphetamine, a dopamine *releaser*. It may be that some dopaminergic activity is required for these behaviours to occur but (unlike in the case of backward walking and circling) abnormally high dopamine release is not necessary. Table 5 summarizes the patterns of dependence of different behavioural syndromes on dopamine and 5-HT suggested by our work.

Amphetamine at high dosage causes schizophrenia-like symptoms in man, including both visual and audi-

Table 4 Behavioural effects of levallorphan alone and together with (+)-amphetamine

	Behavioural scores					
	Hind limb abduction body shake	*Backward walking*	*Pivoting*	*Rearing*	*Gnawing/licking*	*Forward walking*
Levallorphan						
15 mg/kg	0	0	0	3.6 ± 0.6	0	4.3 ± 0.1
25 mg/kg	2.4 ± 0.8	3.2 ± 0.6	2.0 ± 0.6	3.3 ± 0.8	0	5.1 ± 0.2
50 mg/kg	3.6 ± 1.0	7.1 ± 0.8	2.4 ± 0.7	5.5 ± 1.1	0	9.2 ± 1.1
50 mg/kg plus amphetamine 1 mg/kg	3.2 ± 0.9	1.3 ± 0.5*	1.2 ± 0.3	8.8 ± 0.9	0	8.9 ± 1.1

General methods as in Table 1. Significance of difference from rats given levallorphan 50 mg/kg only: $*P < 0.01$.

Table 5 Optimal requirements for different dopamine and 5-hydroxytryptamine (5-HT)-dependent behaviours

Dopamine activity	*5-HT activity*	*Behaviour*
High	High	Backward walking, circling.
High	Low	Rearing, gnawing, licking.
Present?	High	Reciprocal forepaw treading, hind-limb abduction, body tremor etc.

tory hallucinations (Snyder, 1973; Woodrow, Reifman & Wyatt, 1978). Furthermore, many other hallucinogens, in common with amphetamine, cause backward walking and circling or pivoting in rats e.g. *p*-methoxyamphetamine, psilocybin, lysergic acid diethylamide (LSD), mescaline and the hallucinogenic morphine mixed agonist/antagonist drugs, cyclazocine, pentazocine and levallorphan (Smythies, Johnston, Bradley, Benington, Morin & Clark, 1967; Schneider, 1968). Some of these drugs may also increase stimulation of both catecholamine and 5-HT receptors e.g. *p*-methoxyamphetamine which releases striatal dopamine and is also a potent releaser of 5-HT (Tseng, Menon & Loh, 1976). Evidence on the mechanism of the above behaviour when caused by LSD is less clear (see review, Boarder, 1977) but agonistic effects on dopamine and 5-HT receptors are indicated respectively by stimulation of adenylate cyclase activity in dopamine-rich brain regions (Spano, Kumakura, Tonon, Govoni & Trabucchi, 1975; Von Hugen, Roberts & Hill, 1975) and 5-HT-like action on spinal 5-HT receptors (Andén, Corrodi & Fuxe, 1971). Furthermore, pentazocine appears to release brain catecholamines and 5-HT as it depletes them without altering their rates of synthesis (Holtzman & Jewett, 1972).

However, other evidence appears not to favour abnormal motor behaviour being mediated by stimulation of both dopamine and 5-HT postsynaptic receptors. Thus pivoting, backward walking, and lateral head movements caused by levallorphan were prevented by α-methyl-*p*-tyrosine, an inhibitor of catecholamine synthesis but, *p*-chlorophenylalanine, an inhibitor of 5-HT synthesis and methysergide, a 5-HT antagonist, had no apparent effect (Phillips & Wray, 1975). Furthermore lateral head movements and pivoting induced by cyclazocine were not prevented by methysergide or various dopamine antagonists (Buckett & Shaw, 1975). Indeed these behaviours following adminstration of either cyclazocine or levallorphan were actually inhibited by amphetamine and by the dopamine agonists, apomorphine and piribedil, at low doses.

Results with levallorphan in the present study agree with these earlier reports. However, there were prominent qualitative differences between levallorphan-induced abnormal motor behaviour and that seen following amphetamine, *p*-chloroamphetamine or fenfluramine. For instance, tight circling was not seen in levallorphan-treated rats and whereas episodes of backward walking occurred they were limited to a few slow ataxic steps. Therefore these results do not necessarily contradict the suggestion that distinctive backward walking and circling requires concurrent activation of dopamine and 5-HT receptors.

As amphetamine and many other hallucinogens provoke abnormal locomotion in laboratory animals it has been suggested that this is a response to hallucination (Davis, Bedford, Buelke, Guinn, Hatoum, Waters, Wilson & Braude, 1978). This raises the possibility that not only catecholamine neurones but also 5-HT neurones are involved in the development of amphetamine psychosis and that backward walking in particular may be worth investigation as a potential animal model for human amphetamine psychosis, and therefore for paranoid schizophrenia which it closely resembles (Snyder, 1973; Woodrow *et al.*, 1978). It could also be relevant to the abnormal voluntary movements seen in most patients with Parkinson's disease under long term treatment with L-DOPA (Barbeau, 1969) which can release 5-HT (Ng, Chase, Colburn & Kopin, 1970) in addition to its more prominent effects on dopamine metabolism.

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