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A PHARMACOLOGICAL ANALYSIS OF THE HYPERACTIVITY SYNDROME INDUCED BY β-PHENYLETHYLAMINE IN THE MOUSE

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1 The effects of the putative 5-hydroxytryptamine (5-HT) receptor antagonists, methysergide, mianserin and methergoline, the dopamine receptor antagonists, haloperidol, thioridazine and clozapine, and the noradrenaline (NA) receptor antagonists, phentolamine, phenoxybenzamine and propranolol on the behavioural responses of mice to β-phenylethylamine (PEA, 75 mg/kg) have been examined.

2 PEA produced a syndrome consisting of three distinct phases. The brief initial phase (0–5 min after injection) which consisted of forward walking, sniffing and headweaving, was succeeded by a locomotor depressant phase (5–20 min after injection) which consisted of abortive grooming, headweaving, splayed hindlimbs, forepaw padding, sniffing and hyperreactivity, and a late locomotor stimulant phase (20–35 min after injection), which was characterized by forward walking, sniffing, hyperreactivity, rearing and licking.

3 Methysergide, mianserin, methergoline, clozapine and propranolol inhibited headweaving and splayed hindlimbs, whereas haloperidol, thioridazine, phentolamine and phenoxybenzamine had no effect on these responses. Forepaw padding was strongly inhibited by methergoline and a high dose of mianserin, and weakly antagonized by methysergide, clozapine, haloperidol and thioridazine. In contrast, padding was mildly potentiated by phenoxybenzamine and phentolamine but strongly potentiated by propranolol. It is proposed that headweaving and splayed hindlimbs are 5-HT-mediated responses whereas forepaw padding also involves 5-HT mechanisms but may be partially due to release of tryptamine.

4 Rearing and licking were inhibited by haloperidol (most strongly), thioridazine and clozapine but potentiated by mianserin, methysergide, propranolol, phenoxybenzamine or phentolamine. Methergoline inhibited licking without affecting rearing. It is suggested that PEA-induced rearing and licking are produced by activation of dopaminergic neurones and inhibited by 5-HT or NA stimulation.

5 Phenoxybenzamine inhibited sniffing and produced backward walking when administered prior to PEA, suggesting mediation by NA of sniffing and an inhibitory influence of NA on backward walking.

6 Clozapine and thioridazine were the most effective antagonists of hyperreactivity and it is proposed that this response is dopamine-mediated. Forward walking was inhibited by high doses of haloperidol or clozapine and potentiated by methergoline, mianserin or methysergide, suggesting that hyperactivity may also be mediated by dopamine but subject to 5-HT inhibition.

7 Abortive grooming was the dominant behavioural component observed after PEA administration and was prevented by all of the antagonists tested which suggests that catecholamine and 5-HT mechanisms may be involved in the expression of this response.

8 Since PEA is an endogenous compound in animals and man, and has been claimed to be present in abnormal amounts in some schizophrenics, PEA-induced behavioural stimulation in mice (which includes the postulated hallucinogenic responses of abortive grooming and backward walking) may be a useful animal model of psychosis.

Introduction

β-Phenylethylamine (PEA), which is an endogenous constituent of the human and rodent brain (Durden, Philips & Boulton, 1973; Boulton, Juorio, Philips & Wu, 1975; Philips, Rozdilsky & Boulton, 1978), has been linked to migraine headaches (Sandler, Bonham-Carter, Goodwin & Ruthven, 1976) and depression (Boulton & Milward, 1971; Sabelli & Mosnaim, 1974), and has been implicated in the aetiology of schizophrenia (Sandler & Reynolds, 1976; Wyatt, Gillin, Stoff, Moja & Tinklenberg,

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1977; Potkin, Karoum, Chuang, Cannon-Spoor, Phillips & Wyatt, 1979). PEA resembles amphetamine in structure and has a similar behavioural profile. Both compounds possess anorectic properties (Cole, 1978; Dourish & Boulton, 1981; Dourish, 1982a) and produce stereotyped behaviour in rats at high doses (Randrup & Munkvad, 1966; 1967; Braestrup & Randrup, 1978; Lyon & Robbins, 1975). PEA is a specific substrate for type B monoamine oxidase (Yang & Neff, 1973) and, therefore, is metabolized extremely rapidly in the brain (Wu & Boulton, 1975; Durden & Philips, 1980). Consequently, a low dose of PEA in combination with a suitable monoamine oxidase inhibitor has been reported to induce behavioural stimulation (Nakajima, Kakimoto & Sano, 1964; Moja, Stoff, Gillin & Wyatt, 1976). In the mouse, PEA alone, or after inhibition of monoamine oxidase, produces a conspicuous hyperactivity syndrome (Nakajima *et al.*, 1964; Jackson, 1978; Dourish, 1982b).

The neurochemical substrates of the behavioural effects of PEA, however, are still uncertain. A number of authors have proposed that PEA has both direct and indirect effects on brain catecholamine systems (Braestrup, Andersen & Randrup, 1975; Borison, Havdala & Diamond, 1977; Jackson, 1978; Borison & Diamond, 1978). However, evidence from experiments in the rat indicates that stereotypy produced by PEA in this species may involve the activation of central 5-hydroxytryptamine (5-HT) mechanisms (Sloviter, Connor & Drust, 1980; Dourish, 1981; Dourish & Dewar, 1982). Further, a recent observational analysis of the behavioural effects of PEA in isolated and aggregated mice revealed the presence of behavioural components which are associated with an increase in brain 5-HT activity (Dourish, 1982b).

The purpose of the present study was to conduct a detailed observational investigation of the neurochemical mechanisms involved in the mediation of PEA-induced hyperactivity in the mouse, using drugs that are thought to act as selective antagonists of the 5-HT, noradrenaline (NA) and dopamine neurotransmitter systems.

Methods

Male Swiss albino mice (18–25 g body weight) were used in the experiments. The animals were housed in hanging wire cages with food and water *ad libitum*. Lighting operated on a 12 h dark/light cycle (lights on 06 h 00 min) and temperature was maintained at 20–22°C. The mice were tested individually since group testing has been reported to potentiate some of the behavioural effects of PEA (Jackson, 1978; Dourish, 1982b). The apparatus and test procedure have previously been described in detail (Dourish, 1982b). Briefly, animals were observed in circular plastic cages and ten individual components of behaviour which are produced or increased by PEA were scored on a 0–4 scale depending on the intensity of the behaviour exhibited. The scoring was that previously employed (Dourish, 1982b): 0 = absent; 1 = mild intensity, present 1–2 times during observation period; 2 = moderate intensity, present 3–4 times; 3 = high intensity, present 5 or more times; 4 = severe, present for prolonged periods. The behavioural components scored were: freezing (inactive), forward walking, rearing, grooming (including abortive grooming), sniffing, backward walking, headweaving (fast side-to-side head movements), forepaw padding (clonic paw movements), hyperreactivity (reactivity to a pencil tap on the cage), and licking. Scores for each animal were determined during alternate 5 min periods until all drug effects had dissipated. Observations were made 'blind' where possible. Mice were randomly allocated to drug treatment conditions and each animal was tested once only. On test days each animal was weighed and placed in a test cage for a 30 min habituation period before any drug treatment. Putative antagonist drugs (or vehicle solutions) were injected 15 or 30 min before a PEA or vehicle injection (see Table 1 for details of drug injection protocols). A dose of 75 mg/kg of PEA was employed in the interaction experiments since this is the minimum dose required to produce a biphasic stimulant effect on activity (Jackson, 1978; Dourish, 1982b). All drug injections were made intraperitoneally.

Mean and median scores were calculated for each behavioural component over the complete test and for each 5 min sample period. Data from antagonist-pretreated groups are expressed as percentages of control values (i.e. PEA 75 mg/kg alone) where applicable. Results were analysed using two non-parametric statistical tests (Siegel, 1956), the Kruskal-Wallis one way analysis of variance, followed by the Mann-Whitney U test (2-tailed) to locate specific group differences.

Results

PEA at a dose of 75 mg/kg produced a biphasic stimulant effect on activity in isolated mice. An initial burst of activity occurred immediately after injection (0–5 min) which was characterized by forward walking or running, sniffing and headweaving. Approximately 5 min after injection the animals exhibited a stereotyped activity syndrome (hereafter referred to as early phase stereotypy) which consisted of locomotor activity depression, abortive grooming (the dominant activity during this phase), forepaw

Table 1 Drugs used in the investigation

Drug	*Dose* (mg/kg)	n	*Solution*	*Pretreatment time prior to PEA* (min)	*Source*
Mianserin HCl	10	5	In distilled water	15	Organon, U.S.A.
	20	6			
Methysergide tartrate	10	6	In distilled water with	15	Sandoz, Canada
	20	6	vigorous shaking		
Methergoline base	7.5	6	By warming in	15	Farmitalia, Italy
	15	6	distilled water		
	20	4			
Haloperidol base	0.1	6	In distilled water with	30	Janssen, Belgium
	0.2	6	a minimum quantity of		
	0.3	4	glacial acetic acid		
Clozapine base	5	6	In distilled water with	30	Sandoz, Canada
	10	6	glacial acetic acid		
Thioridazine Ch	5	10	In distilled water	30	Sandoz, Canada
	10	4			
Phentolamine HCl	10	6	In distilled water	15	Ciba-Geigy, Canada
	20	6			
Phenoxybenzamine HCl	10	6	In distilled water	15	Smith, Kline and
	20	6			French, Canada
(−)-Propranolol	10	6	In distilled water	15	ICI, U.K.
	20	6			
β-Phenylethylamine HCl (PEA)	75	14	In distilled water	—	Sigma, U.S.A.

padding, headweaving, splayed hindlimbs, sniffing and hyperrreactivity. Finally, 20–25 min post-injection the animals became more active and began to walk around the cage sniffing, rearing and repetitively licking the cage walls or floor (referred to as late phase stereotypy; see Table 2 and Dourish, 1982b).

The effects of 5-hydroxytryptamine and catecholamine antagonists on headweaving, forepaw padding and splayed hindlimbs

PEA-induced headweaving was significantly decreased by mianserin and methysergide at both doses tested. In contrast, methergoline antagonized headweaving only at the highest dose used (20 mg/kg) and had little or no effect at doses of 7.5 or 15 mg/kg (see Figure 1a). Headweaving was also antagonized by clozapine and propranolol, and by a high (20 mg/kg) dose of phenoxybenzamine which induced mild sedation (see Figure 1b and c). Haloperidol (0.1 or 0.2 mg/kg), thioridazine (5 mg/kg), phentolamine (10 or 20 mg/kg), and phenoxybenzamine (10 mg/kg) had no significant effect on headweaving. Higher doses of haloperidol (0.3 mg/kg) and thioridazine (10 mg/kg) partially antagonized headweaving although this effect was not statistically significant (see Figure 1b). The high dose of haloperidol, however, also induced sedation. Forepaw padding was prevented by methergoline at doses of 7.5 or 15 mg/kg and mianserin at a dose of 20 mg/kg (see Figure 2a). Although these were the only statistically significant effects of 5-HT blockade, all other doses of 5-HT antagonists tested showed a trend to reduce padding intensity. Similarly, neuroleptic pretreatment attenuated padding in a number of instances, but none of the reductions were significant (see Figure 2b). In contrast, adrenoceptor blockade potentiated forepaw padding. The most significant effect was observed after a dose of 20 mg/kg of propranolol (values attained were 200% of control, see Figure 2c).

The appearance of splayed hindlimbs was prevented by a 5-HT antagonist, propranolol or clozapine, pretreatment ($P < 0.05$ in all cases, Mann-Whitney U test) but unaffected by α-adrenoceptor blockade, or pretreatment with haloperidol or thioridazine.

Table 2 The effect of an intraperitoneal injection of β-phenylethylamine (75 mg/kg) on activity in the mouse

Behavioural component	*Time post injection* (min) 0–5	10–15	20–25	30–35
Freezing	2.71	0**	0**	0**
Forward walking	3.78	1.78*	2.0 *	2.3 *
Rearing	0.5	1.36	1.38	1.8*
Grooming	2.28	2.57	3.15*	2.8
Sniffing	3.85	4.0	4.0	3.9
Backward walking	0	0.14	0.15	0.2
Headweaving	3.28	3.57	3.07	3
Padding	0.64	2.21*	1.84	1.4
Hyperreactivity	1.14	1.64	2.46*	2.4*
Licking	0	1.74**	2.76**	2.4**

Each value is a median score from 14 animals on a 0–4 scale (see method for details). Levels of significance refer to 2-tailed Mann-Whitney U test comparisons between 0–5 min time sample and other time samples: $*P<0.05$; $**P<0.01$.

The effects of 5-hydroxytryptamine and catecholamine antagonists on rearing, licking, hyperreactivity and forward walking

Rearing was generally increased by blockade of NA or 5-HT receptors and inhibited by neuroleptic pretreatment. Propranolol increased rearing scores to 250% of control. Similarly, rearing was strongly potentiated by phenoxybenzamine (10 mg/kg), mianserin (20 mg/kg) and methysergide (10 or 20 mg/kg, see Figure 3a and c). A low dose of methergoline (7.5 mg/kg) increased rearing whereas higher doses (15 or 20 mg/kg) produced a small decrease in the behaviour (see Figure 3a). Haloperidol pretreatment decreased rearing, to less than 40% of control values, at all doses tested (see Figure 3b). Similarly thioridazine at a dose of 10 mg/kg virtually abolished rearing. A lower dose of thioridazine, however, or clozapine (5 or 10 mg/kg) produced no significant effect on this behaviour (see Figure 3b).

Antagonist effects on licking were qualitatively similar to the observed effects on rearing. NA blockade potentiated licking although this was a non-significant trend in most cases. The exception was propranolol at a dose of 20 mg/kg (see Figure 4c). Mianserin and methysergide had no significant effect on licking although in most cases scores were greater than control values. In contrast, methergoline significantly decreased licking (see Figure 4a). Similar-

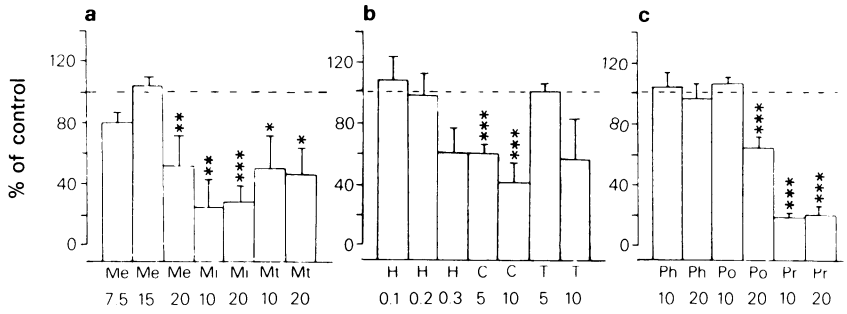

Figure 1 Effect of drugs with predominantly 5-hydroxytryptamine antagonist, dopamine antagonist or noradrenaline antagonist properties on headweaving elicited by 75 mg/kg of β-phenylethylamine (PEA) in mice. Data are mean percentage of control response (i.e. PEA alone); vertical lines show s.e.mean. (a) Me = methergoline; Mi = mianserin; Mt = methysergide; (b) H = haloperidol; C = clozapine; T = thioridazine; (c) Ph = phentolamine; Po = phenoxybenzamine; Pr = propranolol. Doses of drugs are mg/kg. Details of behavioural ratings and numbers of subjects tested are in Methods. Statistical comparisons were made by 2-tailed Mann Whitney U test: $*P<0.05$; $**P<0.02$; $***P<0.01$.

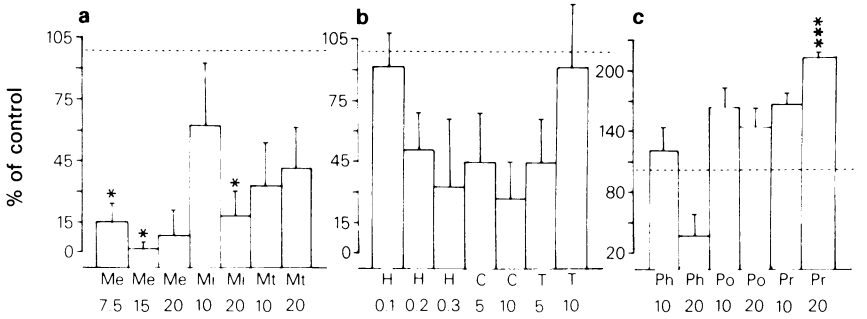

Figure 2 Effect of drugs with predominantly 5-hydroxytryptamine antagonist, dopamine antagonist or noradrenaline antagonist properties on forepaw padding elicited by 75 mg/kg of β-phenylethylamine. Details are as described in Figure 1.

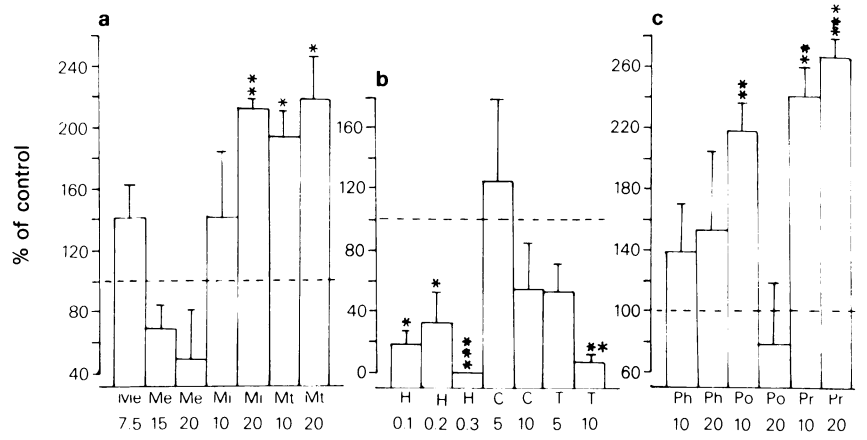

Figure 3 Effect of drugs with predominantly 5-hydroxytryptamine antagonist, dopamine antagonist or noradrenaline antagonist properties on rearing elicited by 75 mg/kg of β-phenylethylamine. Details are as described in Figure 1.

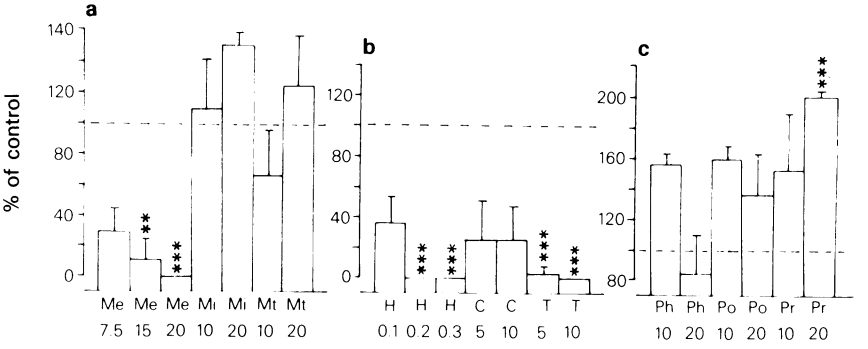

Figure 4 Effect of drugs with predominantly 5-hydroxytryptamine antagonist, dopamine antagonist or noradrenaline antagonist properties on licking elicited by 75 mg/kg of β-phenylethylamine. Details are as described in Figure 1.

ly, neuroleptic pretreatment reduced or abolished licking in all cases (see Figure 4b). Neuroleptic administration also tended to decrease hyperreactivity (see Figure 5b). The most effective blockers of hyperreactivity were clozapine and thioridiazine. Methergoline, at all doses tested, and mianserin (10 mg/kg) also showed a trend to decrease reactivity, although the methergoline antagonism was not statistically significant (see Figure 5a). NA blockade generally exhibited little effect on hyperreactivity with the notable exception of a 20 mg/kg dose of phenoxybenzamine or a 10 mg/kg dose of propranolol (significant depression of reactivity, see Figure 5c). Forward walking and running was generally increased by 5-HT antagonists, unaffected by adrenoceptor antagonists, and decreased or unaffected by neuroleptics (see Figure 6). Methysergide at doses of 10 or 20 mg/kg and methergoline at a dose of 7.5 mg/kg significantly potentiated forward walking and running. In contrast, haloperidol (0.3 mg/kg) and thioridazine (10 mg/kg) prevented walking and induced sedation. Freezing intensity showed a consistent inverse relationship to forward walking and, therefore, these data are not presented.

The effect of 5-hydroxytryptamine and catecholamine antagonists on abortive grooming, backward walking and sniffing

Abortive grooming and sniffing were the dominant responses during the PEA-induced hyperactivity syndrome. The grooming behaviour consisted of compulsive cleaning movements which were termed abortive as the mouse often failed to complete the action by touching its body. On occasions grooming was so intense that the animal lost balance and fell backwards while pawing at its body. Abortive grooming was effectively abolished by all the antagonist pretreatments (5-HT, dopamine or NA antagonists) at all dose levels used ($P<0.01$ in all cases, 2-tailed Mann-Whitney U test).

Backward walking was rarely observed in mice treated with PEA (75 mg/kg) alone. Pretreatment with a 20 mg/kg dose of phenoxybenzamine, however, initiated consistent 'mild intensity' backward walking ($P<0.01$, Mann-Whitney U test comparison between phenoxybenzamine pretreated group and PEA control).

Sniffing was unaffected by all antagonist pretreatments with the exception of phenoxybenzamine which significantly reduced the behaviour ($P<0.01$, Mann-Whitney U test). None of the antagonists tested (with the notable exception of propranolol) had any significant effect on the duration of the PEA-induced hyperactivity syndrome. Pretreatment with propranolol at a dose of 10 mg/kg increased the duration of behavioural stimulation by 5–10 min ($P<0.05$, independent, 2-tailed t test), while a dose of 20 mg/kg of propranolol prolonged the syndrome by 20–25 min ($P<0.01$, t test). The most prominent behavioural components observed during the prolonged stimulation were sniffing, rearing, licking and padding against the cage walls.

Discussion

The present results confirm the previous finding that the intraperitoneal administration of PEA produces a biphasic stimulant effect on activity in mice (Jackson, 1972; Dourish, 1982b). The PEA hyperactivity syndrome appears to consist of three phases, each of

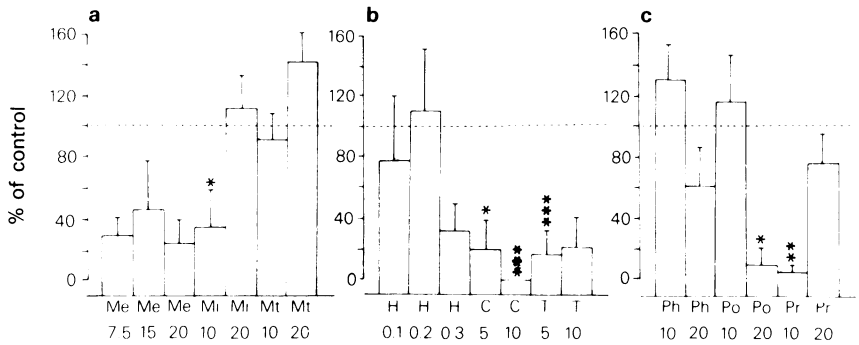

Figure 5 Effect of drugs with predominantly 5-hydroxytryptamine antagonist, dopamine antagonist or noradrenaline antagonist properties on hyperreactivity elicited by 75 mg/kg of β-phenylethylamine. Details are as described in Figure 1.

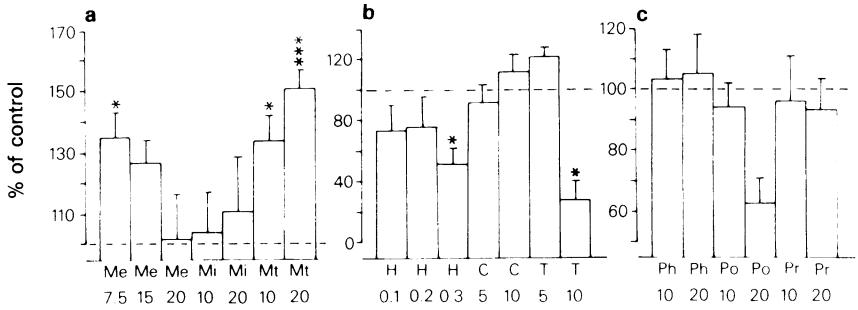

Figure 6 Effect of drugs with predominantly 5-hydroxytryptamine antagonist, dopamine antagonist or noradrenaline antagonist properties on forward walking elicited by 75 mg/kg of β-phenylethylamine. Details are as described in Figure 1.

which is characterized by a distinct group of behavioural components (Dourish, 1982b; see present results). A biphasic stimulant effect of PEA on activity was first described by Jackson (1972, 1974) in grouped mice. Data generated by photobeam interruptions showed an initial increase in activity counts (0–5 min post-injection), followed by a depression (5–20 min), and a late stimulation of activity (20–35 min). Jackson's quantitative data are in good agreement with the present results and previous findings in this laboratory (Dourish, 1982b).

It has been proposed that early phase stimulation is dependent on an intact synthetic pathway for NA and dopamine, and also involves both dopamine and NA receptors, since it is blocked by dopamine β-hydroxylase inhibitors, α-methyl *p*-tyrosine, and catecholamine antagonists, but not reserpine (Jackson, 1975). In contrast, Jackson (1978) suggests that late phase activity stimulation, which is blocked only by high doses of dopamine antagonists, is due to a direct agonist action on post-synaptic dopamine receptors, and may be mediated by a deaminated metabolite of PEA, rather than the amine itself.

The present results are in general agreement with Jackson's hypothesis, since NA or dopamine blockers do exhibit profound effects on various aspects of PEA-induced hyperactivity. The data obtained also point to the involvement of indoleaminergic mechanisms in the PEA-induced syndrome, however, particularly with regard to early phase stereotypy.

Effects of antagonists on early phase stereotypy

The major effects of the putative antagonists on the PEA syndrome are summarized and simplified in Table 3. It can be seen that headweaving was antagonized by 5-HT blockade, but generally unaffected by α-adrenoceptor antagonists or the neuroleptics, haloperidol and thioridazine, suggesting 5-HT mediation of this response. The dopamine

Table 3 Summary of the effects of putative antagonist drugs on the behavioural syndrome induced by β-phenylethylamine (75 mg/kg) in mice

	Behavioural components								
Antagonist	H	SP	PD	R	L	HYP	FW	SN	G
Haloperidol	0	0	− or 0	− −	− −	− or 0	−	0	− −
Clozapine	− −	− −	−	− or +	−	− −	0	0	− −
Thioridazine	0	0	− or 0	− −	− −	− −	− or 0	0	− −
Methergoline	−	− −	− −	0	− −	−	+	0	− −
Mianserin	− −	− −	−	+ +	+ or 0	− or 0	0	0	− −
Methysergide	− −	− −	−	+ +	+ or 0	+ or 0	+ +	0	− −
Phentolamine	0	0	0	+	+ or 0	0	0	0	− −
Phenoxybenzamine	0	0	+	+ + or 0	+	− or 0	− or 0	− −	− −
Propranolol	− −	− −	+ +	+ +	+ +	− or 0	0	0	− −

H = headweaving; SP = splayed hindlimbs; PD = forepaw padding; R = rearing; L = licking; HYP = hyperreactivity; FW = forward walking; SN = sniffing; G = grooming (including abortive grooming).
+ + = strong protentiation; + = slight potentiation; 0 = no effect; − = slight inhibition; − − = strong inhibition.

antagonist, clozapine and the β-adrenoceptor blocker, propranolol, both prevented headweaving at all doses tested. However, this finding is consistent with 5-HT-mediation of headweaving since both drugs are thought to block 5-HT receptors in addition to their well established catecholamine blocking properties (Green & Grahame-Smith, 1976; Weinstock, Weiss & Gitter, 1977; Leysen, Niemegeers, Tollenaere & Laduron, 1978; Fernando, Lees & Curzon, 1980, Dourish, 1981). Similarly, the appearance of splayed hindlimbs was prevented by 5-HT antagonists, clozapine or propranolol, but unaffected by haloperidol, thioridazine or α-adrenoceptor antagonists. The present results also suggest that indoleaminergic mechanisms may mediate PEA-induced clonic forepaw padding (see Table 3).

Headweaving, forepaw padding and splayed hindlimbs, have been referred to as the 5-HT behavioural syndrome and are widely used as an index of central 5-HT activity (Grahame-Smith, 1971; Jacobs, 1976; Sloviter, Drust & Connor, 1978). The present results are consistent with the hypothesis that headweaving and splayed hindlimbs reflect 5-HT stimulation since these behaviours were selectively antagonized by 5-HT blockers (including clozapine and propranolol) but largely unaffected by haloperidol, thioridazine or α-adrenoceptor blockers. There appears to be evidence, however, for the possible involvement of an amine (or amines) other than 5-HT in the expression of forepaw padding. Padding was strongly potentiated by adrenoceptor blockade which suggests that stimulation of NA mechanisms by PEA may inhibit the full expression of this behaviour. In addition, blockade of dopamine receptors tended to reduce padding intensity, indicating a possible dopamine involvement. Methergoline, however, was the most effective antagonist of forepaw padding. Although methergoline has been proposed as a specific 5-HT antagonist (Fuxe, Agnati & Everitt, 1975), it has been demonstrated that tryptamine-mediated effects are more sensitive to its antagonist action (Clineschmidt & Lotti, 1974; Cox, Lee & Martin, 1981). This is consistent with the recent report that in neurophysiological studies, methergoline was able to block depressant responses to iontophoretically applied tryptamine at doses that did not affect responses to 5-HT (Jones, 1982). Since PEA, at high dose levels, can release both tryptamine and 5-HT *in vitro* (Jones, personal communication), it appears possible that forepaw padding could be partly due to tryptamine release whereas headweaving and splayed hindlimbs are likely to be 5-HT-dependent. Interestingly, recent studies have indicated that tryptamine may be partly responsible for the behavioural syndrome seen after administration of the monoamine oxidase inhibitor tranylcypromine plus L-tryptophan (Crow & Deakin, 1977; Marsden & Curzon, 1978). However, since multiple receptors for 5-HT have been identified in the brain by binding studies (Whitaker & Seeman, 1978; Peroutka & Snyder, 1981; Nelson, Herbert, Enjalbert, Bockaert & Hamon, 1980) an alternative explanation of the discrepancy in antagonist blockade of padding, headweaving and splayed hindlimbs is the possibility of a PEA agonist action at two distinct 5-HT receptors.

Effects of antagonists on late phase stereotypy

The effects of putative antagonist drugs on the dominant late phase behavioural components were qualitatively similar (see Table 3), indicating that rearing and licking are probably mediated by a common mechanism. Rearing and licking were prevented by dopamine blockers (N.B. licking was also inhibited by methergoline) but unaffected or potentiated by 5-HT or adrenoceptor blockade. These results suggest that activation of adrenergic (especially β-adrenergic) or 5-HT mechanisms has an inhibitory effect on rearing and licking which are probably produced by dopaminergic stimulation. This is consistent with the report that NA release inhibits the expression of PEA-induced licking in the rat (Mogilnicka & Braestrup, 1976). Consequently, administration of phenoxybenzamine or the dopamine β-hydroxylase inhibitor, FLA-63, changed PEA-induced sniffing into gnawing and licking (Mogilnicka & Braestrup, 1976). Furthermore, bilateral 6-hydroxydopamine lesions of the ascending NA neurones produced the same result (Braestrup, 1977).

The blockade of licking by methergoline appears to be inconsistent with the drug's established antagonistic effects on tryptamine and 5-HT. A recent report, however, indicates that methergoline also has dopamine antagonist properties (Spano, Biggo, Casu, Gessa, Bareggi, Grovini & Trabucchi, 1978) and this may explain the observed blockade of licking.

Hyperactivity and hyperreactivity associated with the 5-HT behavioural syndrome in the rat have generally been attributed to dopaminergic stimulation (Green & Grahame-Smith, 1974; Dourish, 1981; Deakin & Dashwood, 1981; Green, Hall & Rees, 1981). In the present study dopamine antagonists prevented hyperreactivity but were less effective in blocking hyperactivity (measured by forward walking, see Figure 6). In contrast, 5-HT blockade had no consistent effect on hyperreactivity but, in most cases, potentiated hyperactivity. These results stand in general agreement with dopamine mediation of reactivity and hyperactivity and also suggest that 5-HT may have an inhibitory influence on the expression of hyperactivity. This is consistent with the recent proposal that 5-HT has inhibitory effects on

the hyperactivity and hyperreactivity produced by tranylcypromine plus L-tryptophan in the rat (Green *et al.*, 1981).

Effects of antagonists on proposed hallucinogenic behaviour and sniffing

Backward walking was rarely observed after PEA administration in this experiment since a 75 mg/kg dose of the drug is below the threshold dose required to elicit this behaviour (Dourish, 1982b). However, when mice were pretreated with phenoxybenzamine PEA consistently induced backward walking. It appears likely that backward walking, in addition to rearing and licking, may be suppressed by PEA-induced release of NA. Fernando and colleagues (1980) have proposed that backward walking produced by high doses of amphetamine in rats is mediated by the simultaneous activation of dopamine and 5-HT systems and it seems likely that backward walking produced by PEA in the mouse may be mediated by a similar mechanism.

Stereotyped sniffing was very prominent during the PEA syndrome and was inhibited only by phenoxybenzamine which suggests that this behavioural component may be mediated by α-adrenoceptor mechanisms. Similarly, abortive grooming was a dominant behaviour during the entire PEA-induced syndrome but was prevented by all the antagonists tested. This suggests that both catecholamines and 5-HT are involved in the mediation of this behaviour. Further experiments using lower doses of the respective antagonists may elucidate the neural substrates of abortive grooming.

The PEA syndrome in mice is dominated by abortive grooming, a behavioural response which is not observed in rats injected with equivalent doses of PEA (Sloviter *et al.*, 1980; Dourish, 1981), and which exhibits sensitization following chronic PEA administration (Dourish, unpublished results). Neuroleptics, particularly clozapine, are the most effective antagonists of the PEA-induced stimulation (see Table 3). Consequently, the hyperactivity syndrome induced by PEA in the mouse may be a more useful animal model of the paranoid state than the chronic PEA stereotypy model (proposed by Borison *et al.*, 1977) in the rat.

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