*Pharmacology Biochemistry & Behavior*, Vol. 25, pp. 711–716, 1986. © Ankho International Inc. Printed in the U.S.A. 0091-3057/86 $3.00 + .00

# A Behavioural and Pharmacological Examination of Phenylethylamine-Induced Anorexia and Hyperactivity—Comparisons With Amphetamine

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POPPLEWELL, D. A., P. J. COFFEY, A. M. J. MONTGOMERY AND M. J. BURTON. *A behavioural and pharmacological examination of phenylethylamine-induced anorexia and hyperactivity–Comparisons with amphetamine.* PHARMACOL BIOCHEM BEHAV **25**(4) 711–716, 1986.—The discovery that trace amine beta-phenylethylamine (PEA) has a number of properties in common with amphetamine (AMPH) has led to the suggestion that PEA may be a neuromodulator of catecholamine release or an "endogenous amphetamine." The present study compared PEA-induced behavioural changes (anorexia and hyperactivity) with AMPH-induced changes in feeding and motor activity. The first experiment examined the effects of PEA (0–35 mg/kg) on the temporal profile of feeding. The results from this experiment revealed important differences between the effects of PEA as compared with AMPH, in particular PEA failed to increase the rate of eating that is characteristic of AMPH-induced anorexia. The second experiment concurrently measured food intake and motor activity following equi-anorectic doses of PEA and AMPH and pretreatment with the neuroleptic pimozide. Pimozide attenuated PEA-induced hyperactivity, AMPH-induced hyperactivity and AMPH-induced anorexia, but failed to attenuate PEA-induced anorexia. These findings are discussed in relation to the possible mechanisms of action of PEA and AMPH.

Feeding Hyperactivity Microstructural analysis Phenylethylamine Amphetamine Pimozide Trace amine

PHENYLETHYLAMINE is a trace amine found in both the rat and human C.N.S., being formed by the decarboxylation of the amino acid phenylalanine [19]. Interest in PEA arose from several reports showing that levels of PEA may be increased in schizophrenic and phenylketonuric patients [13,14] and decreased in depressed patients [12].

PEA is structurally similar to amphetamine (AMPH), only lacking the alpha-methyl group, and pharmacological studies have shown that PEA and AMPH have similar properties (see [6] for review). For example, both PEA and AMPH release catecholamines from presynaptic stores [2] and block their reuptake [3]. Such findings have led to the suggestion that PEA may be an endogenous AMPH [17], or a neuromodulator of CA release [3].

In terms of their gross behavioural effects, PEA and AMPH have a number of characteristics in common. In particular, AMPH and PEA have been shown to produce hyperactivity and anorexia in the laboratory rat [7,10]. However, the potency and duration of action of PEA are much less than those of AMPH, probably because PEA is metabolised more rapidly [18]. Detailed analysis of the pharmacological and behavioural effects of PEA on motor activity have also revealed differences between PEA and AMPH [9].

The purpose of the present study was to explore further the behavioural effects of PEA, in particular PEA-induced anorexia and hyperactivity, and to compare these with the effects of AMPH.

## EXPERIMENT 1: THE EFFECTS OF PEA ON THE TEMPORAL PROFILE OF FEEDING

When the laboratory rat is allowed access to food it feeds in relatively discrete periods ('bouts') separated by periods of nonfeeding ('interbout gaps'). AMPH-induced anorexia is associated with specific changes in the characteristics of these bouts, i.e., reduced bout duration, bout size and increased eating rate [1], and these changes differ from those seen following the administration of other anorectic agents, e.g., fenfluramine [5]. The first experiment was therefore

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TABLE 1

THE EFFECT OF PEA ON FEEDING BOUT PARAMETERS IN THE FIRST 0.5 HR OF RECORDING

| | PEA (mg/kg) | | | | |
|---|---|---|---|---|---|
| | 0 | 15 | 25 | 35 | F-value |
| Total Intake (g) | 9.45 (0.75) | 6.11† (0.85) | 5.05† (0.50) | 1.9† (0.55) | 22.80 |
| Total Time (min) | 14.55 (1.4) | 11.73* (1.67) | 9.73† (0.87) | 3.8† (1.1) | 20.56 |
| Bout Freq (no) | 9.38 (1.65) | 6.14† (0.97) | 6.75* (0.95) | 3.5† (0.95) | 8.01 |
| Bout Size (g) | 1.04 (1.6) | 1.16 (2.43) | 0.79 (0.93) | 0.63* (1.68) | 2.93 |
| Median IPI (sec) | 3.72 (0.19) | 4.48 (0.78) | 5.46 (0.99) | 5.94 (1.14) | 2.06 |

Each score is the mean and standard error of the mean (parentheses) for 8 animals. IPI=interpellet interval.

Differences between control (i.e., 0) and specific injection conditions were assessed using one-way analysis of variance, $df=3, 21$ (the F-values for which are included in the table), followed by Dunnett's test ($df=21$).

*$p<0.05$, †$p<0.01$—as compared with saline control.

designed to examine the effects of PEA on the temporal profile of feeding, and to explore the possibility that PEA-induced anorexia is associated with the same changes in feeding bouts as AMPH.

## METHOD

Eight male Lister hooded rats (324–427 g) (University of Sussex stock) were housed in groups of four and habituated to the conditions of the experiment for 7 days, i.e., 3 hr food (lab chow) access per day (14 hr 00 min to 17 hr 00 min), a 12 hr L/D cycle (lights off 14 hr 00 min), and the injection schedule. All animals were allowed ad lib access to water throughout the experiment and were weighed and handled every day.

Following this habituation period, and for the remainder of the experiment, each animal was transferred to a separate experimental box at the beginning of food access and returned to its home cage at the end of the 3 hr feeding period. The animals were allowed a further 7 days to habituate to these conditions.

The details of the apparatus box have been described elsewhere [5]. In brief, each experimental box contained a food dispenser that delivered 45 mg (Campden) food pellets and a water dispenser. A microcomputer recorded the removal of each 45 mg food pellet and coded it in terms of the box (animal) number and the time since the beginning of the experiment (to 0.1 sec resolution). Subsequent analysis then divided these records into interpellet intervals (i.e., time intervals separating the removal of consecutive pellets), bouts and interbout gaps (see the Analysis section). A detailed description of the temporal profile of feeding was thus obtained for each rat under each experimental condition.

### *Procedure*

All injections were given immediately before food access and the recording of food intake lasted for the full 3 hr feeding period. There were four injection conditions: (1) vehicle (distilled water), (2) 15 mg/kg PEA, (3) 25 mg/kg PEA, (4) 35 mg/kg PEA. (These doses of PEA were shown in pilot studies to produce a comparable degree of anorexia, over 0.5 hr, to that seen following 0.5 to 1.0 mg/kg d-AMPH. They were injected immediately before food access since PEA has a relatively short half life.) PEA (Sigma Ltd) was dissolved in

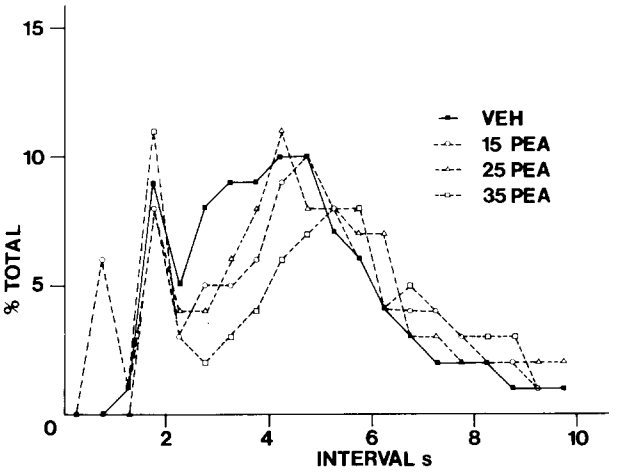


FIG. 1. The frequency distribution of interpellet intervals under each PEA condition during the first 0.5 hr of recording. Each bin represents the pooled intervals for 8 animals expressed as a percentage of the total number of intervals for that condition. Note the relative decrease in interpellet intervals between 2 to 5 seconds following PEA administration.

TABLE 2

THE EFFECT OF D-AMPHETAMINE ON FEEDING BOUT PARAMETERS IN THE FIRST 0.5 HR OF RECORDING

| | AMPH (mg/kg) | | | |
|---|---|---|---|---|
| | 0 | 0.5 | 1.0 | F-value |
| Total Intake (g) | 10.34 (0.88) | 3.95† (0.52) | 1.6† (0.58) | 54.58 |
| Total Time (min) | 18.03 (1.15) | 6.29† (0.78) | 2.29† (0.76) | 106.71 |
| Bout Freq (no) | 7.88 (1.24) | 5.75* (0.53) | 4.13† (1.38) | 4.50 |
| Bout Size (g) | 1.59 (0.32) | 0.70† (0.10) | 0.47† (0.11) | 8.09 |
| Bout Duration (min) | 2.79 (0.57) | 1.11† (0.14) | 0.68† (0.19) | 9.13 |
| Median IPI (s) | 4.06 (0.09) | 3.20† (0.34) | 2.36† (0.18) | 11.17 |

Each score is the mean and standard error of the mean (parentheses) for 8 animals. IPI=interpellet interval.

Differences between control (i.e., 0) and specific injection conditions were assessed using one-way analysis of variance, $df=3, 21$ (the F-values for which are included in the table), followed by Dunnett's test ($df=21$).

*$p<0.05$, †$p<0.01$—as compared with saline control.

TABLE 3

THE TIMES FOR INJECTIONS AND FOOD ACCESS FOR THE FOUR GROUPS IN EXPERIMENT 2 (SEE TEXT)

| | Injection 1 | Injection 2 | Food Access |
|---|---|---|---|
| Group 1 | 10 h 15 min | 12 h 10 min | 12 h 15 min |
| Group 2 | 11 h 10 min | 13 h 05 min | 13 h 10 min |
| Group 3 | 12 h 05 min | 14 h 00 min | 14 h 05 min |
| Group 4 | 13 h 00 min | 14 h 55 min | 15 h 00 min |

'Injection 1' refers to vehicle/pimozide injection, 'Injection 2' to vehicle/PEA/AMPH injection, 'Food Access' to the start time for 3 hr food access. The 12 hr dark period of the L/D cycle for each group began at the same time as the start of food access.

distilled water and injected at a concentration of 25 mg/ml (IP). Each animal received all conditions, 72 hr separated each injection condition, and the orders of injections were counterbalanced.

*Analysis*

The log survivorship curve for the combined IPIs for the vehicle condition was used to divide the feeding records of each animal into bouts and interbout gaps (see [5]). A similar analysis using separate log survivor curves for each subject produced the same profile of drug-induced changes.

The data from the first 0.5 hr of recording for each subject under each condition were analysed to yield the following bout parameters: (1) bout frequency, i.e., number of bouts; (2) mean bout size; (3) mean bout duration; (4) eating rate, i.e., median interpellet interval within bouts. The latter measure is less susceptible to changes brought about by infrequent short or long interpellet intervals than a similar measure calculated by dividing bout size by bout duration.

*Statistical Analysis*

Changes in total food intake and bout parameters were analysed using a one-way analysis of variance, data being grouped according to injection condition. Where appropriate, differences between control and experimental conditions were examined using Dunnett's test [32] (see the Results section).

## RESULTS

PEA produced a dose-dependent reduction in food intake over the first 0.5 hr of recording, $F(3,21)=22.8$, $p<0.001$ (see Table 1).

This anorexia was associated with reductions in bout frequency, $F(3,21)=8.01$, $p<0.005$, and total time within bouts, $F(3,21)=20.56$, $p<0.001$ (see Table 1). Overall analysis of variance just failed to reveal any change in bout size, $F(3,21)=2.93$, $p<0.10$, but subsequent analysis using Dunnett's test revealed a reduction in bout size following 35 mg/kg PEA ($r=0.41$, $df=3,21$, $p<0.05$, two-tailed).

Median interpellet interval within bouts was increased by all doses of PEA (see Table 1), although again this failed to achieve overall statistical significance, $F(3,21)=2.06$, $p<0.20$.

This tendency towards an increase in median interpellet interval was explored further by examining the frequency distribution of interpellet intervals for the four injection conditions (see Fig. 1). PEA produced a relative decrease in interpellet intervals between 2–5 seconds, i.e., over an interpellet interval range that has a relatively high frequency in control animals.

## DISCUSSION

These results confirm the finding that PEA acts as an anorectic agent [10] and extend previous work to show that relatively low doses of PEA produce a dose-dependent reduction in food intake in food-deprived animals.

As with PEA-induced hyperactivity and hypodipsia [7], PEA-induced anorexia is short-lived, perhaps reflecting the finding that the drug is rapidly metabolised.

Microstructural analysis of feeding following PEA revealed differences between PEA-induced and AMPH-induced anorexia. Notably, AMPH increases eating rate [1], but PEA does not (see Table 1 and Table 2). This suggests that the two agents produce anorexia by different neurochemical mechanisms. Reports [1] that AMPH-induced increases in eating rate are attenuated by neuroleptic pretreatment support our suggestion that PEA and AMPH induce anorexia through different neurochemical mechanisms. (The same subjects were used in a follow-up study to examine the effects of 0.5 mg/kg and 1.0 mg/kg AMPH upon the microstructure of feeding, under identical conditions to those for PEA in Experiment 1. Although the results from this experiment must be interpreted with caution, since the same subjects were used as for Experiment 1, the profile of feeding seen following AMPH was identical, in all major respects, to that reported in other studies (see [1] and Table 2).

# EXPERIMENT 2: THE CONCURRENT MEASUREMENT OF LOCOMOTOR ACTIVITY AND FOOD INTAKE FOLLOWING AMPH AND PEA ADMINISTRATION AND THE EFFECTS OF PIMOZIDE PRETREATMENT

The first experiment showed that AMPH and PEA produce different changes in the behavioural profiles of feeding, indicating that AMPH and PEA may differ in terms of their neurochemical actions. As described above (see the Introduction) PEA and AMPH are characterised by their effects on both feeding and locomotor behaviour, in particular both produce hyperactivity and anorexia in the laboratory rat [7,10]. Further, the finding that AMPH-induced anorexia and hyperactivity are attenuated by neuroleptic pretreatment supports the view that AMPH acts at central dopamine receptors (e.g., see [1,6]).

The purpose of the second experiment was to test the hypothesis that PEA-induced changes in feeding and locomotor activity, like AMPH, are attenuated by neuroleptic pretreatment.

## METHOD

Twelve male hooded Lister rats (296–337 g) (University of Sussex stock) were divided into 4 groups of 3 and habituated to the conditions of the experment, i.e., a 12 hr L/D cycle, 3 hr access to food (45 mg Campden food pellets) per day, and the injection schedule. All animals were allowed ad lib access to water throughout the experiment and were handled every day. Since there were only 3 experimental boxes available each group was habituated and run at different times of the day (see Table 3 for details).

Following this habituation period, and for the remainder

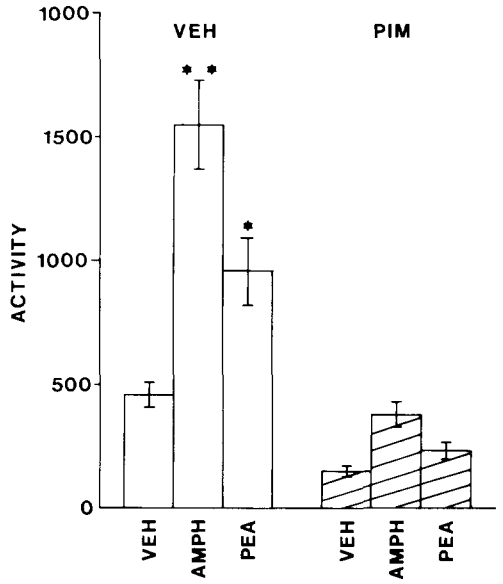


FIG. 2. Total activity during the first 0.5 hr of recording following vehicle (VEH), PEA or AMPH administration, and pretreatment with pimozide (PIM) or vehicle (VEH). Each block is the mean and standard error of the mean (bars) for 8 animals. Differences between specific injection conditions were analysed using Tukey's HSD test. $^{**}p<0.01$ as compared with vehicle control (two-tailed).

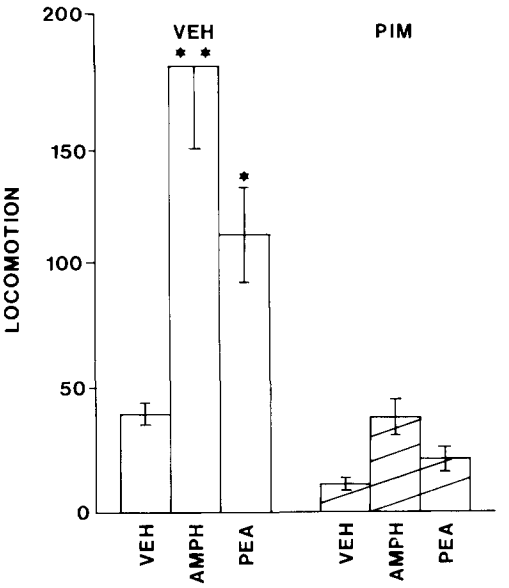


FIG. 3. Total locomotion during the first 0.5 hr of recording following vehicle (VEH), PEA or AMPH administration, and pretreatment with pimozide (PIM) or vehicle (VEH). Each block represents the mean and standard error of the mean (bars) for 8 animals. Differences between specific injection conditions were analysed using Tukey's HSD test. $^{**}p<0.01$ as compared with vehicle control (two-tailed).

of the experiment, each animal was transferred to a separate experimental box at the beginning of food access and their locomotor activity and food intake recorded for the first 0.5 hr of food access. They were then transferred to individual cages for the remainder of the 3 hr food access period, during which time 45 mg food pellets (Campden Ltd) were available. They were then returned to their home cages. The animals were allowed a further 7 days to habituate to these conditions.

The experimental boxes were adapted from a design by Ljundberg and Ungerstedt [16] and consisted of an open field area (69×69×25 cm), in which the animals could move freely, a food dispenser that delivered 45 mg food pellets (Campden Ltd) and a water bottle (see Experiment 1). Ten infrared emitters and detectors (Radio Spares Ltd) were placed symmetrically around the outside of the cage, 35 mm above the cage floor. A microcomputer recorded the removal of each 45 mg food pellet and interruption of each light beam, coding it in terms of event type (i.e., pellet removal or beam interruption), box (animal) number and time since the beginning of the experiment (to 0.1 sec resolution). Beam interruptions were additionally encoded so as to identify the order in which they occurred.

*Procedure*

On injection days, each animal received an injection of either pimozide (0.5 mg/kg, IP) or vehicle (0.3% w/v tartaric acid, IP) 2 hours prior to food access. Immediately before food access an injection of either AMPH (1 mg/kg, IP), PEA (35 mg/kg, IP) or vehicle (distilled water, IP) was administered. Pimozide was dissolved in warm 0.3% w/v tartaric acid at a concentration of 0.5 mg/ml, AMPH was dissolved in distilled water (1.0 mg/ml) and PEA in distilled water (35 mg/ml). Each animal received all conditions, 72 hr separated each test day, and the orders of injection conditions were counterbalanced.

*Analysis*

The analysis of the temporal patterning of feeding was identical to that for Experiment 1, except the data were analysed using a two-way analysis of variance (i.e., pimozide-vehicle versus PEA-AMPH) followed by Tukey's HSD test [4].

Activity was expressed in terms of 'total activity' and 'total locomotion' for each animal under each injection condition as defined by Ljungberg and Ungerstedt [16]. Briefly, total activity is defined as the total number of beam interruptions, whereas total locomotion is a subset of this and represents ambulation around the cage. Both of these measures were analysed separately using two-way analysis of variance (i.e., pimozide-vehicle versus PEA-AMPH), followed by Tukey's HSD test.

## RESULTS

*Activity*

The results of the analysis of variance revealed a statistically significant interaction between the stimulant conditions (i.e., VEH, PEA and AMPH) and the pretreatment conditions (VEH and PIM), for both total activity and locomotion (ACT: $F(2,22)=12.41$, $p<0.001$, two-tailed test; LOCO: $F(2,22)=8.302$, $p<0.01$, two-tailed test). Post-hoc tests revealed that these interactions were due to PEA and AMPH being statistically significantly higher than VEH condition following VEH pretreatment but not following PIM pretreatment. In other words, PIM blocked AMPH and PEA-

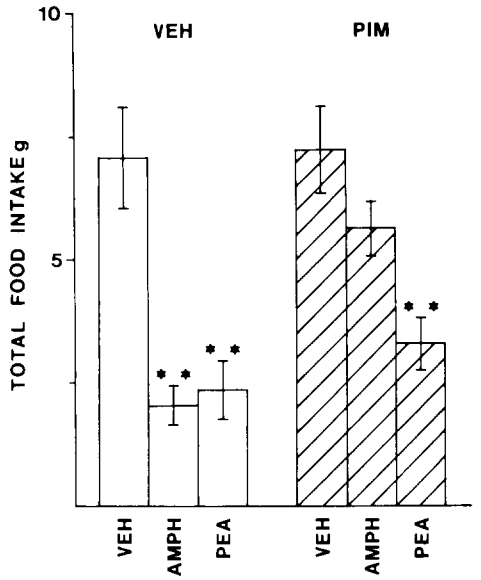


FIG. 4. Total food intake during the first 0.5 hr of recording following vehicle (VEH), PEA and AMPH administration, and pretreatment with pimozide (PIM) or vehicle (VEH). Each block represents the mean and standard error of the mean (bars) for 8 animals. Differences between specific injection conditions were analysed using Tukey's HSD test. *$p<0.05$ as compared with vehicle control (two-tailed). **$p<0.01$ as compared with vehicle control (two-tailed).

induced increases in total activity and locomotion (see Figs. 2 and 3).

*Food Intake*

As with activity, a statistically significant interaction between stimulant conditions and blocker conditions occurred, $F(2,22)=4.97$, $p<0.025$, two-tailed test).

The results of the post-hoc tests showed that AMPH and PEA, without pimozide pretreatment, produced reductions in food intake, confirming the results of Experiment 1. However, in contrast to the results for activity, pimozide pretreatment had differential effects on AMPH-induced and PEA-induced anorexia, i.e., pimozide pretreatment statistically significantly attenuated AMPH-induced anorexia but did not attenuate PEA-induced anorexia (AMPH: $F(1,55)=16.977$, $p<0.001$, PEA: $F(1,55)=1.26$, n.s., see Fig. 4).

The analysis of the temporal patterning of feeding revealed substantial inter-animal variability in the bout parameters, e.g., mean bout size vehicle + vehicle condition=1.28 g (standard error=0.12 g), vehicle + AMPH condition=0.85 g (standard error=0.22 g), vehicle + PEA condition=0.82 g (standard error=0.18 g). It was not possible, therefore, to compare the temporal patterning in Experiment 2 to the results found in Experiment 1 (see the Discussion section below).

## DISCUSSION

The finding that AMPH-induced hyperactivity and anorexia are blocked by neuroleptic pretreatment is well documented [1] and confirms the reliability of the methods and procedure employed in the present study.

The results for PEA-induced and AMPH-induced hyperactivity support the hypothesis that PEA and AMPH produce behavioural stimulation by similar modes of action. In particular, both PEA and AMPH cause substantial increases in locomotion, i.e., ambulation around the cage, in addition to increases in overall activity, and pretreatment with the neuroleptic pimozide will block both PEA-induced and AMPH-induced hyperactivity. Taken together these results suggest that PEA-induced hyperactivity is predominantly brought about by stimulation of dopamine systems within the central nervous system (see the General Discussion section).

In contrast to the results for activity, the effects of pimozide pretreatment on PEA-induced and AMPH-induced anorexia (i.e., AMPH-induced anorexia attenuated and PEA-induced anorexia unaffected) suggest that the two agents produce anorexia by different mechanisms, possibly different neurochemical mechanisms. A number of alternative explanations for this result are considered below (see the General Discussion section).

The relatively large variability in the temporal patterning of feeding found in Experiment 2, as compared with Experiment 1, is a result that we have consistently found using the activity boxes in other experiments. It is possible that this resulted from the larger cages used in Experiment 2.

## GENERAL DISCUSSION

In summary, the major findings of the present study were as follows: (1) Treatment with PEA resulted in a dose-dependent suppression of food consumption, similar to that seen following treatment with AMPH. (2) PEA-induced anorexia, unlike AMPH-induced anorexia, was not associated with an increase in eating rate, i.e., decrease in median interpellet interval. (3) Pimozide pretreatment failed to attenuate PEA-induced anorexia, even at a dose that did attenuate AMPH-induced anorexia. (4) Both PEA-induced hyperactivity and AMPH-induced hyperactivity were blocked by pimozide pretreatment.

It is apparent that both PEA and AMPH treatment results in enhanced motor activity and reduced feeding behaviour. Pretreatment with pimozide blocked both PEA-induced and AMPH-induced hyperactivity, suggesting that both of these effects are dependent upon stimulation of postsynaptic pimozide-sensitive DA receptors.

There were, however, a number of differences between the effects of PEA and AMPH on consummatory behaviour. For example, AMPH reduces interpellet interval, but PEA tends to increase interpellet interval. These observations show that the anorectic actions of PEA and AMPH result from changes in different microstructural parameters, suggesting the possibility that the two drugs reduce feeding through different neurochemical mechanisms. This suggestion is further supported by our finding that, unlike AMPH-induced anorexia, PEA-induced anorexia is not blocked by pimozide pretreatment.

Alternatively, it is possible that the behavioural actions of both drugs are mediated via changes in the same neurochemical system, but that functionally dissimilar doses of AMPH and PEA were compared. It is well documented that the behavioural effects of AMPH differ considerably depending upon the dose administered: For example, low doses produce hyperlocomotion and higher doses produce stereotyped behaviour, probably by different neurochemical mechanisms (see [6]). However, in the present study an explanation of this type would seem inappropriate since both drugs were equated in terms of their anorectic potency, and

both compounds produced similar increases in locomotion and activity (see Experiment 2).

A second possible alternative explanation is that the dose of pimozide used in Experiment 2 was either too small to block PEA-induced anorexia, or was too high and suppressed feeding behaviour. However, neither of these explanations are likely since PEA-induced hyperactivity, AMPH-induced hyperactivity and AMPH-induced anorexia were attenuated by pimozide pretreatment, whereas PEA-induced anorexia was not. Furthermore, several other (unpublished) studies carried-out in this laboratory have failed to attenuated PEA-induced anorexia in the rat with pimozide pretreatment.

Inspection of the relevant literature suggests that central DA receptors, primarily in the nigrostriatal and mesolimbic systems, play an important role in the mediation of AMPH-induced locomotion and anorexia (see [6]). The results of the present study, with regard to PEA-induced hyperactivity, therefore indirectly support the view that systemic PEA produces hyperactivity by acting upon central DA receptors. Conversely, the failure of pimozide pretreatment to block PEA-induced anorexia indicates that the effects of PEA on feeding are mediated by some neurochemical system other than pimozide-sensitive DA receptors.

Evidence from Experiment 1 may provide some clues as to what caused the PEA-induced anorexia. Namely, PEA-induced anorexia was associated with a tendency towards increased interpellet intervals (i.e., a reduction in bout feeding rate, see Fig. 1). This pattern of feeding is qualitatively similar to the pattern seen following treatments which enhance central 5-HT transmission [5], so it is possible that PEA-induced anorexia may also be mediated via enhanced central 5-HT activity. Further support for this suggestion is provided by two studies. Firstly, reductions in 24-hr feeding following 100 mg/kg PEA have been partially attenuated by pretreatment with a 5-HT antagonist, methysergide [8]. Secondly, results presented by Dyck [11] suggest that there may be a complex interaction between DA and 5-HT following treatment with PEA on 24-hr feeding.

In conclusion, the dissociation found in the present study between the effect of PEA and AMPH on feeding behaviour is consistent with *in vivo* PEA and AMPH having different modes of action.

ACKNOWLEDGEMENTS

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