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Characterisation of Adjustments to the Structure of Feeding Behaviour following Pharmacological Treatment: Effects of Amphetamine and Fenfluramine and the Antagonism Produced by Pimozide and Methergoline

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BLUNDELL, J. E. AND C. J. LATHAM. *Characterisation of adjustments to the structure of feeding behaviour following pharmacological treatment: Effects of amphetamine and fenfluramine and the antagonism produced by pimozide and methergoline*. PHARMAC. BIOCHEM. BEHAV. 12(5) 717–722, 1980.—An observational procedure for examining the micro-structure of eating has been employed to establish the characteristic behaviour patterns displayed after various pharmacological manipulations. Using a double dissociation design it was shown that amphetamine and fenfluramine gave rise to quite distinctive readjustments to the structure of feeding behaviour. Amphetamine anorexia was characterised by a long initial delay, following which feeding was typified by infrequent short bursts of rapid eating. These effects were antagonised by the dopamine receptor blocking agent, pimozide. Fenfluramine exerted a more restricted pattern of action characterised by a marked slowing of the rate of eating. This effect was countered by the serotonin receptor blocking agent methergoline. These data throw light on the way in which pharmacological agents may impede food consumption and upon the neurochemical systems believed to be involved in the expression of feeding behaviour.

Eating Amphetamine Fenfluramine Pimozide Methergoline Antagonism Serotonin Dopamine

THE eating behaviour of rats and mice is represented by a sequence of activities in which episodes (bouts) of eating are interspersed with bouts of non-eating activities (e.g. [27]). When eating is suppressed various alterations may occur in the organisation of this behaviour sequence including, *inter alia*, a delay in the onset of the first eating bout, reductions in the number, duration or size of the eating bouts, alterations in the local rate of eating within eating bouts, or the occurrence of a premature cessation of the feeding sequence [6]. These features have been referred to as adjustments to the initiation, maintenance or termination of the feeding process [11]. In turn, different types of pharmacological agents which inhibit food consumption have been shown to exert different types of effects upon the behavioural sequence of feeding. For example, in deprived animals whose food consumption is continuously monitored by an automated eatometer amphetamine reduces food intake, in part, by delaying the onset of eating; on the other hand after fenfluramine administration eating begins normally but the feeding process is brought to an early halt [8]. In addition, when the micro-structure of eating has been examined by exhaustive classification of behaviour from continuous video-taped recordings of feeding sequences, various pharmacological treatments have been shown to bring about alterations to the internal structure of bouts within the feeding sequence. One of the most interesting adjustments is to the local (intra-bout) rate of eating which is slowed by a number of compounds including fenfluramine, certain agents which inhibit the re-uptake of serotonin, pimozide [5] and 5-hydroxytryptophan [7]. Paradoxically, the local rate of eating is enhanced by a moderate dose of amphetamine which markedly suppresses total food consumption. These data have been used to suggest ways in which intended manipulations of various neurotransmitter systems such as serotonin [2,3] or dopamine [4] may intervene in the expression of feeding behaviour.

In the last few years pharmacological research strategies

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in feeding have made frequent use of the drugs amphetamine and fenfluramine, and it has been suggested that these compounds can be used conjointly as a drug-pair to investigate mechanisms controlling food intake [10, 20, 21]. These drugs differ not only in their behavioural effects but also in their actions upon neurotransmitters and bodily metabolism [19]. In general it is known that the effect of peripherally administered amphetamine on food consumption can be antagonised by prior administration of dopamine receptor blockers such as pimozide, haloperidol, α-flupenthixol and others [13, 19, 22] whilst the effect of fenfluramine can be attenuated by certain serotonin receptor blocking drugs including cyproheptadine, methysergide and methergoline (e.g. [9, 14, 19]). In turn, these pharmacological studies suggest mechanisms for the observed effects of amphetamine and fenfluramine on the elements of the feeding sequence. Although the major effects of these two drugs appear to be mediated by these particular neurotransmitters, it is known that both amphetamine and fenfluramine exert effects on a number of neurotransmitter systems including catecholamines, serotonin and acetylcholine. Accordingly, the present investigation was carried out to examine further the adjustments to the organisation of feeding behaviour brought about by amphetamine and fenfluramine, and to characterise these changes through the use of appropriate receptor blocking agents. The study was designed to throw light on the identity of micro-regulatory controls over eating [17].

METHOD

Animals

Male hooded Lister rats (280–310 g) were housed in single cages in a quiet environment with a 12-hr light/dark cycle. For 10 days prior to the start of the experimental treatments the rats were exposed to a feeding cycle of 18-hr deprivation followed by free access to food for 32 hr. In addition, the rats were handled daily and also received two sham intraperitoneal injections at times corresponding to subsequent drug administration. These procedures were adopted in order to acclimatise animals to all novel and stressful features of the experiment before the period of data collection.

Design and Procedure

At the start of the experiment the animals were randomly sorted into two groups, one of which was to be used to examine the effects of amphetamine and pimozide whilst the other group received injections of fenfluramine and methergoline. The study conformed to a 2×2 repeated measures design in which each animal (in each group) served as its own control and received each of the four experimental treatments in turn. The rats received two injections prior to each testing period. In the amphetamine group the first injection was given at 4 hr prior to the test session at which time the rats received a dose of 0.45 mg/kg pimozide or the injection vehicle (a buffered solution of tartaric acid). This time interval was chosen since it has been shown that pimozide becomes maximally effective as a dopamine blocker between 2 and 8 hr after administration [26]. The second injection (30 min before the test) was of 0.9% w/v saline or 1.0 mg/kg d-amphetamine sulphate. For the fenfluramine group, the first injection of saline or 2.0 mg/kg methergoline was given 60 min prior to the test and the second injection of saline or 3.0 mg/kg dl-fenfluramine hydrochloride was given 30 min later. These doses of amphetamine and fenfluramine were chosen on the basis of earlier experiments in this laboratory showing an equivalent reduction in food intake for a 1 hr test session. The doses of pimozide and methergoline were chosen for their capacity to antagonise these reductions in food intake. The experiment was designed to reveal the specific behavioural changes responsible for these reductions in food consumption by amphetamine and fenfluramine, and their reversal by pimozide and methergoline respectively. Each rat received four different combinations of drug treatments and these were administered in a counterbalanced order according to two latin squares. A minimum period of 72 hr intervened between successive test sessions.

At the time of the second injection the animal's cage was removed from the rack and placed in a position where the rat's activities could be clearly observed. Subsequently, during the one hour feeding test the rat's behaviour was continuously observed and recorded by a trained observer. In addition, the feeding session was recorded on video-tape by means of a television camera located behind and above the observer. This precaution was adopted so that any ambiguity arising in the categorisation of the rat's behaviour could be resolved immediately after the test by consulting the video-tape record. This record was also used to establish the reliability of the observations. The animal's activities were exhaustively classified into six categories—eating, drinking, locomotion, sedation, grooming and miscellaneous—and the observer recorded the onset, duration and termination of these behavioural events by depressing buttons on a control panel linked to a six-channel event recorder. The data collected in this way were later processed to provide the following parameters of eating behaviour: latency to the onset of eating, total duration of time spent eating, number of separate bouts of eating, duration of eating bouts and the local rate of eating. This final measure refers to the rate at which each rat consumed food when in the act of eating, and should be distinguished from the overall rate which could be computed simply by dividing the amount of food consumed by the time allocated for the feeding test. In addition, computations also revealed the number of occasions on which the animals were observed to be moving or stationary, or engaging in drinking or grooming together with the amount of time spent on each of these activities.

All of the observations in this study, together with the computation of data were carried out under double blind conditions. The observer who recorded the behaviour of the animals and carried out computations on the data was not in any way involved in the preparation or the administration of the drugs. The data were analysed by a parametric analysis of variance procedure for repeated measures.

RESULTS

The results for the effects of amphetamine on feeding parameters are shown in Table 1. Column 1 of this table confirms that amphetamine strikingly reduced the amount of food consumed in the 1 hr test, $F(1,7)=20.6$, $p<0.001$. The main effect for the pimozide treatment was not significant, $F(1,7)=4.18$, but a significant amphetamine×pimozide interaction was observed, $F(1,7)=16.6$, $p<0.01$. This interaction indicates that pimozide antagonised the effect of amphetamine on the amount of food eaten. Similar effects were revealed for the measure of latency to begin eating. Amphetamine markedly delayed the onset of eating, $F(1,7)=27.6$, $p<0.001$, but the pimozide treatment had no

TABLE 1

EFFECT OF AMPHETAMINE AND PIMOZIDE TREATMENTS ON VARIOUS PARAMETERS OF FEEDING BEHAVIOUR. FIGURES IN THE BODY OF THE TABLE ARE MEAN VALUES (N=8) AND STANDARD ERRORS

Drug treatment		Feeding parameters				
1st injection	2nd injection	Food intake (g)	Eating time (min)	Latency (min)	No. of eating bouts (N)	Local eating rate (g/min)
Vehicle	Saline	6.2 ±0.5	22.4 ±2.9	1.8 ±0.6	28.0 ±7.0	0.29 ±0.03
Pimozide	Saline	6.0 ±0.5	32.5 ±3.4	1.2 ±0.3	31.9 ±5.0	0.19 ±0.01
Vehicle	Amphetamine	2.5 ±0.4	8.1 ±1.6	19.4 ±5.8	13.7 ±3.1	0.34 ±0.06
Pimozide	Amphetamine	5.3 ±0.7	21.0 ±3.6	6.9 ±4.1	13.4 ±2.2	0.26 ±0.02

TABLE 2

EFFECT OF FENFLURAMINE AND METHERGOLINE TREATMENTS ON VARIOUS PARAMETERS OF FEEDING BEHAVIOUR. FIGURES IN THE BODY OF THE TABLE ARE MEAN VALUES (N=8) AND STANDARD ERRORS

Drug treatment		Feeding parameters				
1st injection	2nd injection	Food intake (g)	Eating time (min)	Latency (min)	No. of eating bouts (N)	Local eating rate (g/min)
Vehicle	Saline	6.8 ±0.5	21.6 ±2.4	2.6 ±1.3	26.9 ±7.2	0.34 ±0.03
Methergoline	Saline	5.0 ±0.5	18.5 ±2.6	1.8 ±0.5	24.1 ±6.3	0.30 ±0.05
Vehicle	Fenfluramine	2.5 ±0.3	18.0 ±2.1	4.0 ±1.7	15.6 ±4.1	0.15 ±0.01
Methergoline	Fenfluramine	4.9 ±0.5	20.9 ±3.0	2.6 ±1.1	27.0 ±6.2	0.25 ±0.03

effect, $F(1,7)=2.20$, whilst the interaction was again significant, $F(1,7)=9.29$, $p<0.05$. With regard to the time spent eating, amphetamine reduced this measure, $(F1,7)=43.8$, $p<0.001$, whilst pimozide markedly increased it, $F(1,7)=24.7$, $p<0.01$. As expected from the data in Table 1, the interaction was not significant. Amphetamine severely reduced the number of observed bouts of eating, $F(1,7)=20.3$, $p<0.01$ but pimozide did not affect this measure, $F(1,7)=0.2$, nor did it influence the action of amphetamine, interaction $F(1,7)=0.9$. A significant main effect of the pimozide pre-treatment was observed on local rate of eating, $F(1,7)=6.5$, $p<0.05$, a finding which was expected since pimozide has previously been shown to markedly slow the eating rate. Although amphetamine administered alone gave rise to a noticeable increase in the rate of eating, the main effect due to the amphetamine condition was not significant, $F(1,7)=3.6$, nor was the pimozide×amphetamine interaction.

Table 2 displays the feeding data for the fenfluramine-methergoline experiment and column 1 indicates that this dose of fenfluramine (3.0 mg/kg) reduced the amount of food consumed to the same level as the 1.0 mg/kg dose of amphetamine. Moreover, the main effect due to the fenfluramine treatment was significant, $F(1,7)=11.6$, $p<0.05$, and there was a significant fenfluramine×methergoline interaction, $F(1,7)=29.6$, $p<0.001$. This interaction indicates that methergoline clearly antagonised the action of fenfluramine on food consumption. The main effect due to methergoline was not significant, $F(1,7)=0.7$.

In contrast to the large number of feeding measures showing significant changes in the amphetamine study (amount, time, latency, bouts and rate), the fenfluramine-methergoline experiment was notable for a general lack of effect on these feeding parameters. Apart from the total amount of food eaten the only other measure influenced by these treatments was the local rate of eating. Fenfluramine gave rise to a severe reduction in eating rate, $F(1,7)=8.07$, $p<0.05$, and there was a significant fenfluramine×methergoline interaction, $F(1,7)=7.89$, $p<0.05$, indicating that methergoline antagonised the action of fenfluramine on the rate of eating.

Naturally, the effects of these pharmacological manipulations on the parameters of eating can only be fully inter-

TABLE 3

EFFECT OF PHARMACOLOGICAL MANIPULATIONS ON NON-FEEDING BEHAVIOURS DISPLAYED DURING THE ONE HOUR TEST SESSION. THE FIRST VALUE REPRESENTS THE MEAN AMOUNT OF TIME (N=8) FOR WHICH ANIMALS ENGAGED IN EACH BEHAVIOUR AND THE FIGURES IN PARENTHESES SHOW THE MEAN NUMBER OF SEPARATE BOUTS OF THAT BEHAVIOUR. FOR THE DRINKING COLUMN, THE SECOND FIGURE INDICATES THE NUMBER OF ANIMALS (MAXIMUM=8) WHICH DRANK DURING THE TEST SESSION

	Behavioural category			
Drug treatment	Activity	Sedation	Grooming	Drinking
Vehicle—saline	19.7 (49.4)	11.5 (6.7)	4.5 (9.6)	1.6–8
Pimozide—saline	13.6 (43.6)	11.1 (7.4)	1.8 (4.1)	1.0–7
Vehicle—amphetamine	43.0 (28.0)	6.6 (8.4)	2.0 (7.6)	0.2–3
Pimozide—amphetamine	15.2 (28.0)	20.4 (16.3)	3.1 (8.9)	0.3–3
Vehicle—saline	20.4 (39.0)	11.9 (6.1)	4.5 (10.6)	1.5–7
Methergoline—saline	19.2 (40.9)	19.6 (10.7)	1.9 (4.6)	0.7–5
Vehicle—fenfluramine	20.5 (29.6)	16.8 (12.0)	4.1 (11.1)	0.6–3
Methergoline—fenfluramine	21.6 (40.6)	16.5 (11.0)	0.4 (2.3)	0.5–2

TABLE 4

MAJOR CHARACTERISTICS OF AMPHETAMINE ANOREXIA OBSERVED IN THE ONE HOUR TEST SESSION FOLLOWING A PERIOD OF FOOD DEPRIVATION. ALSO SHOWN IS THE REVERSAL OF THESE EFFECTS BY PIMOZIDE

Behavioural features of amphetamine anorexia	Antagonism by pimozide
1. Reduction in the amount of food consumed	Yes
2. Long latency to the initiation of eating	Yes
3. Decrease in total time spent eating	Yes
4. Decreased number of separate eating bouts	No
5. Tendency to increase rate of eating	Yes

preted by considering the effects of the drugs on other categories of behaviour. Table 3 shows how the various drug treatments influenced the way in which the animals allocated time to non-eating behaviours. For activity, there was a significant main effect brought about by the amphetamine treatment, $F(1,7)=21.1, p<0.01$, a significant main effect due to the pimozide pretreatment, $F(1,7)=15.2$, $p<0.01$, and a significant pimozide×amphetamine interaction, $F(1,7)=26.0$, $p<0.01$. These data indicate that amphetamine increased the amount of time for which animals displayed locomotor activity whilst pimozide reduced activity time. In addition, pimozide antagonised the effect of amphetamine on this measure. However, it should be noted that pimozide did not influence the action of amphetamine treatment on the number of bouts of activity. A similar effect was noted earlier for eating bouts. In contrast to the clear effects of amphetamine and pimozide on the measure of activity, in the fenfluramine-methergoline experiment no statistically significant adjustments were observed in this behavioural category.

No main effects were observed for drug actions on the behavioural responses making up the category labelled sedation (animal sitting or lying still) but a statistically significant pimozide×amphetamine interaction was revealed, $F(1,7)=6.3$, $p<0.05$. This effect was unexpected and indicated that pimozide brought about an exaggerated reversal of the reduction in sedation shown by amphetamine. No significant effects were observed in the fenfluramine-methergoline experiment. For grooming, no effects were observed in the amphetamine-pimozide study, but there was a significant main effect due to the methergoline pretreatment, $F(1,7)=8.3$, $p<0.05$. In the analysis of time spent drinking, main effects were observed for the amphetamine treatment, $F(1,7)=7.3$, $p<0.05$, for the methergoline pre-treatment, $F(1,7)=11.7$, $p<0.05$, and for the fenfluramine treatment, $F(1,7)=9.1, p<0.05$. It is noticeable that, in contrast to food consumption, pimozide did not antagonise the effect of amphetamine on drinking nor did methergoline counter the action of fenfluramine.

DISCUSSION

The results of this study indicate that there are characteristic behavioural patterns associated with the capacity of different pharmacological manipulations to inhibit food consumption. During the course of short test sessions using animals which had been subjected to a prior period of food deprivation, the only similarity observed between amphetamine and fenfluramine was the tendency to reduce the total weight of food consumed. These data support previous assertions that these two drugs act through differing neurochemical mechanisms and suggest that these compounds intervene in different sets of processes responsible for the organisation of feeding behaviour.

For amphetamine the predominant features have been summarised in Table 4; also included is a summary of the capacity of pimozide to antagonise these behavioural adjustments. The features described in this table, which have been objectively classified, are quite consistent with subjective impressions gained by less thorough observations of amphetamine-treated rats. The animals typically show a long initial delay in starting to eat, following which feeding is characterised by infrequent short bursts of quite rapid eating. The impression is of an animal eating in a hasty and slightly frantic manner, with the eating episodes broken up by periods of locomotor activity. The range of feeding parameters influenced by amphetamine treatment suggests that the drug may be exerting some non-specific effect on the natural arrangement of the elements of feeding behaviour. In turn, this proposition questions whether the anorexia resulting from peripheral administration of amphetamine is largely a result of the drug intervening in a natural system which serves to match an organism's food intake to its nutritional requirements, or whether the anorexia results mainly from a more general disorganisation of behaviour. The effects observed in the present study are consistent with previous work indicating that amphetamine gives rise to a disruption of normal behaviour sequences characterised by a random initiation of episodes of behaviour [25]. It is quite possible that an amphetamine-treated rat is motivated to eat but is unable to articulate behavioural responses required to express this motivation. Under certain circumstances it would appear as if motivation was impaired owing to the fact that motivational strength is often evaluated by an animal's capacity to display behaviour sequences appropriate to the assumed underlying state. The proposal that amphetamine gives rise to a defect in the assembly of behaviour sequences appropriate for feeding is in keeping with the theory of amphetamine action set out by Lyon and Robbins [24] which suggests that, in general, an amphetamine-treated animal "will tend to exhibit increasing response rates within a decreasing number of response categories." Of course, it should be recognised that these comments apply only to peripherally administered amphetamine which has widespread effects on many brain processes, and need not throw any light on the effects of amphetamine observed when administered locally to specific brain loci [23].

It is worth considering whether the adjustment to the elements of feeding behaviour brought about by amphetamine can be related to its action on neurotransmitters. Typically, the major actions of amphetamine are interpreted by reference to the involvement of adrenergic and/or dopaminergic systems [1, 4, 15, 16]. In the present study, it was noticeable that many of the characteristic features of amphetamine were antagonised by pimozide. Consequently, to the extent that this antagonism implies a common dopaminergic mechanism for the actions of the two compounds, it can be argued that certain characteristic behavioural features of the action of amphetamine are mediated via alterations in dopamine systems. One prominent way in which amphetamine disrupts the natural feeding sequence is by preventing the onset of eating, an effect which was clearly reversed by pimozide. It is worth noting that pimozide also counters the latency to begin food hoarding displayed by amphetamine [12]. Moreover, it is clear from a comparison of the data in Tables 1 and 3 that during the period leading up to the commencement of eating amphetamine-treated rats display a high level of locomotor activity, a behavioural feature which is also reversed by pimozide. These findings invite the interpretation that with this particular dose of amphetamine the initiation of eating is displaced by locomotor activity, and pimozide pre-treatment allows eating to begin earlier by severely curtailing the activity-inducing effect of amphetamine. Indeed, the summarised data in Table 3 suggest that pimozide exerts a normalizing effect on the disruption of feeding behaviour brought about by amphetamine. The exception to this tendency is the measure of number of eating bouts (Table 1). Although pimozide markedly increased the amount of time that amphetamine-treated rats spent eating there was no increase in the number of separate episodes devoted to eating. A similar effect was apparent for the activity data. Amphetamine gave rise to an increase in total activity time but a decrease in activity bouts (Table 3); pimozide reduced activity time but had no effect on the number of bouts. The effects of amphetamine alone are quite consistent with one major tenet of Lyon and Robbin's hypothesis [24] that the drug reduces the number of behavioural response categories. However, pimozide pretreatment did not alter this parameter but influenced the amount of time allocated to a particular behaviour (eating and locomotor activity) within separate behavioural episodes. In turn this suggests that the initiation of episodes of behaviour or the switching from one category to another appears not to be mediated by dopaminergic mechanisms.

In contrast to the comprehensive influence of amphetamine on the various elements of feeding behaviour, fenfluramine exerted a far more restricted pattern of action. Indeed, although this dose of fenfluramine gave rise to suppression of food consumption equivalent to that brought about by amphetamine, only one parameter of feeding behaviour, namely the local rate of eating, was markedly affected. Fenfluramine had no statistically significant effect on the latency to begin eating, total eating time or average number of eating bouts; nor was there any significant effect on the amount of time allocated to activity or sedentary behaviour. Consequently, a rat treated with this particular dose of fenfluramine appears to preserve the normal organisation of feeding behaviour but the animal displays a very slow rate of eating once a piece of food has been seized. A significant fenfluramine×methergoline interaction indicated that methergoline antagonised the slow rate of eating induced by fenfluramine. In turn this suggests that the reduced rate of eating was mediated by a serotonergic mechanism.

It is clear, however, that this slow eating rate per se in fenfluramine-treated rats cannot account for the reduction in food consumed. This can be deduced by comparing the behavioural profile for fenfluramine with the profile for pimozide which also reduced eating rate. However, in pimozide-treated rats the slow rate of eating was compensated for by an increase in total eating time so that the total amount of food consumed was not noticeably reduced. After fenfluramine administration the rats did not increase their eating time. This suggests that some feature of fenfluramine's action is limiting food consumption independently of the effect on eating rate. Following fenfluramine injections low food intake and a slow rate of eating occur together but it appears that the slow rate of eating does not cause the low intake. Consequently, whereas the action of pimozide can be interpreted as a function of the animal's capacity to appropriately articulate a behaviour sequence, the action of fenfluramine suggests an intervention in some process to curtail consumption. This process could be located in the periphery (e.g. slowing of gastric emptying) or in the brain (e.g. activa-

tion of a forebrain serotonin pathway). It remains to be demonstrated whether the slow eating rates brought about by fenfluramine and by pimozide are ultimately mediated by a common mechanism, though there is an anatomical basis for considering an interaction between serotonin and dopamine systems [18].

The results of the present study have revealed clear differences between the behavioural profiles of equi-anorectic doses of amphetamine and fenfluramine. The findings suggest that the reduction in food intake seen after amphetamine administration can be understood as an interruption of normal feeding responses due to the drug's actions on the organisation of behaviour sequences. In turn, this interpretation suggests that amphetamine should no longer be considered as a reference drug in the pharmacology of anorexia. However, this view does not preclude the possibility that amphetamine does exert an additional and independent effect on feeding via action upon some central feeding mechanism (e.g. [23]).

For fenfluramine, the marked slowing of eating rate and the reduced intake contained within an otherwise normal behaviour pattern suggest that the drug may intervene directly into one of the many mechanisms which serve to limit food consumption. Moreover, the pharmacological reversal of these drug-induced effects suggest ways in which the manipulation of dopamine and serotonin systems may influence the processes involved in feeding behaviour.

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