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Effects of Anorectic Drugs and Prior Feeding on Food-Rewarded Runway Behavior

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THURLBY, P. L. AND R. SAMANIN. *Effects of anorectic drugs and prior feeding on food-rewarded runway behavior.* PHARMAC. BIOCHEM. BHEAV. 14(6) 799–804, 1981.—Two treatments that act through central catecholamine pathways and are normally found to be strongly anorectic (d-amphetamine, 1.25 mg/kg and diethylpropion, 5.00 mg/kg) failed to influence either latency to run or running velocity in single trial running for food reward. In contrast, d-fenfluramine (2.5 mg/kg), which normally has similar anorectic potency but acts via a serotoninergic mechanism, significantly increased latency and decreased running velocity. Prior feeding (30 min ad lib access to food) also decreased runway performance to a similar degree. Further studies, using a 3 trial procedure where rats were allowed to feed for 30 sec following each run, revealed that d-amphetamine (1.25 mg/kg), both with and without penfluridol pretreatment (2.5 mg/kg), failed to affect running velocity or the amount of food eaten. However, d-fenfluramine (2.5 mg/kg) and a postsynaptic serotonin receptor agonist, m-chlorophenylpiperazine (1.0, 2.0 mg/kg) led to a significant reduction in these measurements. Thus it appears that "serotoninergic" anorectic drugs, like the state induced by prefeeding, depress food-rewarded runway behavior whereas "catecholaminergic" anorectic agents lack such effects.

Amphetamine Fenfluramine Diethylpropion m-Chlorophenylpiperazine Feeding
Runway behavior Motivation Anorexia

ALTHOUGH feeding is a complex behavior the tests commonly employed in the study of its suppression have been remarkably simple. The anorectic potency of pharmacological manipulations is usually characterized solely on the basis of a single measurement, the quantity of the normal diet eaten in a given period by animals which have previously been deprived of food. Theoretically, however, anorexia might be brought about in a variety of ways which could be separated if appropriate experimental conditions were used.

Since it is now clear that in the CNS both catecholaminergic and serotoninergic pathways are involved in the mediation of feeding behavior [18] it is tempting to speculate that the type of anorexia that results from drugs that interact with the catecholaminergic system (e.g., amphetamine) differs in some respect from the type of anorexia produced by drugs that interact with serotonin (e.g., fenfluramine).

From studies of the micro-structure of eating, it has been suggested that amphetamine may reduce food intake by a direct reduction of 'hunger' whereas fenfluramine may act by enhancing satiety mechanisms once eating is in progress [4]. Further work using this technique, where factors such as latency to eat, meal frequency, meal size and local eating rate were measured, has revealed that anorectic drugs can indeed be shown to affect eating in different ways [3]. However, the simple hunger versus satiety hypothesis for the catecholaminergic and serotoninergic systems was not clearly evident from these data.

Other differences have also been found. For example, in rats allowed to self-select diets differing in protein content it has been reported that fenfluramine and fluoxetine, two anorectic agents interacting with serotonin, depress energy intake to a far greater extent than protein intake. This is in contrast to amphetamine which leads to an equivalent reduction in the intake of both protein and energy [22]. The only other situation in which the two classes of anorectic drugs have been shown to differ is with respect to the suppression of feeding during tail-pinch. Amphetamine is not particularly effective in blocking feeding in these circumstances but fenfluramine retains its anorectic properties [1].

The present work has sought to find an additional behavioral test related to feeding in which it may be possible to dissociate treatments that result in a similar degree of anorexia when food intake alone is considered. Normal feeding in response to food deprivation is a 'motivated' behavior and consequently animals may be trained to perform tasks in order to obtain food [15]. The possibility arises that some anorectic drugs may affect feeding before it has even started by reducing the motivation or 'drive' to eat, whilst others may involve normal hunger and motivation to eat but with the anorexia brought about by other means, for example by interfering with the ability to execute the normal mechanical sequence of eating, by the augmentation of competing behaviours or by an enhanced satiety in response to the food being eaten. For this reason it seems logical to investigate the ef-

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fects of anorectic drugs on the motivation to eat, since different modes of anorexia could be separated in this way.

A common experimental procedure that has been used to investigate motivation is a system that provides food delivery in response to lever-press [13, 14, 16]. By using appropriate schedules of food delivery, work the experimental animal is prepared to do in order to obtain food can be determined. However, this system presents certain problems: for example, even low levels of motor excitation tend to disrupt the lever-pressing. A simpler method that may be used to study the strength of the motivation for food is the straight runway [2, 6, 9, 20]. Rats may be trained to run down the runway in order to obtain food placed in a goal area at its end. The level of motivation is indicated by the latency to run after the start box door is opened and in particular by the speed of running to the goal area. An added advantage of this system is that the initial feeding episode may also be monitored. In contrast to lever-press the runway provides the opportunity to monitor a more natural food-oriented behavior, that of a normal mode of locomotion to a region of food availability. In addition, minor locomotor disturbances are not particularly disruptive.

The present study provides evidence suggesting that anorectic drugs such as fenfluramine that act through the serotoninergic system depress the motivation to eat, as revealed by runway performance and the initial eating behavior after arriving at the food. In contrast normally anorectic doses of drugs that influence catecholaminergic mechanisms, such as amphetamine and diethylpropion, do not significantly reduce the apparent motivation of hungry animals for food.

METHOD

Animals

Male CD-COBS (Charles River, Italy) rats initially weighing 175–200 g served as the experimental subjects. They were housed under conditions of constant temperature (21±1°C) and relative humidity (50%) with a 12 hr light–12 hr dark cycle (dark period commencing at 19.30). The rats were caged in groups of four and every day 70 g of food was placed in each cage at 18.30. Using this procedure the animals reached approximately 70–80% of their free feeding weight at the time of the initiation of runway training and weighed about 300 g at the time of testing.

Runway Apparatus and Training

The runway was constructed of chipboard and was internally 10 cm wide and 10 cm in height. The top was a metal grill, allowing the animals to be observed in all parts of the apparatus. The startbox region was 30 cm long and was separated from the runway by a black plastic guillotine gate. The running time was measured from a start point 12 cm in front of this gate to a stop point 20 cm before the goal, a petri dish containing 45 mg Noyes pellets (P.J. Noyes Company, Inc., Lancaster, NH). The measured running distance from start to stop points was 150 cm. These two times were measured using hand-held stopwatches (precision 0.1 sec), by two separate observers. Latency to run was taken as the time from opening the start box gate to the time the rat reached the start point of the runway. The observer of the running time was unaware of the drug treatment received by each rat. Training was based on an established procedure [12] and consisted of four habituation sessions followed by ten days of training. For habituation the rats were placed, four at a time, into the runway for a period of 10 min and allowed free access to food pellets in the goal area. During training the rats were given each day three trials with an intertrial interval of about 5 min. Each trial involved placing the rat in the start box and opening the gate after 10 sec. The rat was then allowed to run to the food and to eat for 15 sec. The animals were found to reach stable latency and running speeds after about twenty trials.

Testing of Runway Performance

The testing of runway performance involved the same procedure as practiced during training. Three experiments were undertaken. In Experiment 1 the effects of d-amphetamine (1.25 mg/kg), d-fenfluramine (2.5 mg/kg) and diethylpropion (2.5, 5.0 mg/kg) on single trial runway performance were investigated and compared to the effect of prefeeding the rats (30 min ad lib intake of normal chow in the home cages immediately prior to testing). Animals failing to run within 1 min were removed from the start box and in such cases a zero running speed was recorded.

In Experiment 2 a three-trial procedure was used with an intertrial interval of 5 min. After running, the animals were allowed access to food for 30 sec. On each trial 20 Noyes pellets were placed in the dish and the number eaten was recorded. The effects of d-amphetamine (1.25 mg/kg) with and without penfluridol pretreatment (2.5 mg/kg) were assessed. In addition, d-fenfluramine (2.5 mg/kg) was investigated using the same three-trial procedure.

Experiment 3 was conducted to characterize the effects of a specific postsynaptic 5HT receptor agonist, m-chlorophenylpiperazine. Three doses were used: 0.5, 1.0 and 2.0 mg/kg following the same procedure as for Experiment 2.

Drug Administration

All drugs were given IP in a volume of 0.2 ml/100 g body weight. The trials were made at a time after drug administration that was in accordance with the pharmacokinetic characteristics of the compounds being studied, as determined previously for the same strain of rat in the same laboratory as the present investigations. For d-amphetamine sulphate (Recordati, Milan, Italy) the first trial was conducted after 30 min (Experiment 1) or 20 min (Experiment 2), for d-fenfluramine hydrochloride (Servier Laboratories, France) after 30 min (Experiment 1) or 40 min (Experiment 2), for diethylpropion hydrochloride (Merrel, Cincinnati, OH) after 30 min (Experiment 1) and for m-chlorophenylpiperazine hydrochloride (EGA-Chemie, West Germany), after 40 min (Experiment 3). Penfluridol (Janssen, Beerse, Belgium) was given *per os*, suspended in a vehicle of 0.5% w/v carboxymethyl cellulose in water, 18 hr before testing. Saline (0.9% w/v sodium chloride) acted as the control injections and was always administered at the same time before testing as the drug under study. All animals were given a saline injection on the day prior to testing in order to reduce the stress resulting from the drug administration.

Statistical Analysis

For all the experiments the design was such that one animal received only a single drug treatment. Running time has been expressed as the running velocity since the latter is normally distributed whereas the former is not. Similarly the

TABLE 1

EFFECTS OF d-AMPHETAMINE, d-FENFLURAMINE, DIETHYLPROPION AND FEEDING ON FOOD-REWARDED RUNWAY BEHAVIOR (MEAN VALUES ± SEM)

Experiment 1 (a) Treatment	Inverse latency (sec^{-1})	Running speed (m/sec)
Saline (n=13)	1.20 ± 0.23	0.63 ± 0.06
d-Amphetamine, 1.25 mg/kg (n=13)	1.46 ± 0.17	0.67 ± 0.05
d-Fenfluramine, 2.5 mg/kg (n=14)	0.37 ± 0.16*‡	0.26 ± 0.06§
Fed, saline (n=14)	0.57 ± 0.18‡	0.35 ± 0.06§
Experiment 1 (b)		
Saline (n=8)	0.99 ± 0.36	0.52 ± 0.08
Diethylpropion, 2.5 mg/kg (n=9)	0.86 ± 0.30	0.58 ± 0.12
Diethylpropion, 5.0 mg/kg (n=8)	1.11 ± 0.28	0.52 ± 0.06

*Significantly different from saline control on the basis of Dunnett's test: †$p<0.05$; ‡$p<0.01$; §$p<0.001$.

latency to run has been converted first to its inverse in order to normalize the data [7]. The statistical significance of the differences between treatment and control means was assessed using Dunnett's test (Experiments 1 and 3) and Student's t-test (Experiment 2).

RESULTS

Experiment 1

The anorectic effects of 2.5 mg/kg d-fenfluramine and 1.25 mg/kg d-amphetamine are found to be similar when assessed by a one hr food intake test in this laboratory, each producing a 50–70% reduction in food intake. These 'equianorectic' doses were compared with regard to their ability to alter runway performance (Table 1). Amphetamine treatment had no significant effect on the latency to run or on the running speed whereas fenfluramine caused an increase in the latency ($p<0.01$) and a marked slowing in the mean running speed to only 41% of the control value ($p<0.001$). Allowing the animals to feed for 30 min prior to testing (food satiated group) also resulted in a similar and significant increase in latency ($p<0.01$) and a reduction in running speed to 56% of the control level ($p<0.001$).

In a separate but identically conducted experiment, the effects of diethylpropion were assesed and the results are also given in Table 1. No significant alterations in either latency or running speed were observed, even at 5 mg/kg which is an effective anorectic dose.

Experiment 2

Penfluridol pre-treatment was used to block the locomotor stimulatory effects of amphetamine but leaving the anorectic effects intact [17]. The runway behavior of rats in this condition has been studied and the results are presented in Table 2. On the first trial no significant differences were found either in latency or in running speed between any of the experimental groups. Penfluridol treatment alone did not alter runway behavior and amphetamine administration in both vehicle and penfluridol treated animals resulted in only a slight non-significant reduction in performance. An increased latency was found on the second ($p<0.01$) and third ($p<0.05$) trials in response to amphetamine administration in the penfluridol treated animals. The same tendency was seen in the vehicle treated rats on the third trial but the difference was not statistically significant. However, nearly normal running speeds were maintained in all the groups for all three trials and no significant differences were found. The amount of food eaten by the animals during the 30 sec in the goal area was also similar for all four experimental groups and the same level of intake was sustained during the three trials.

The effects of d-fenfluramine (2.5 mg/kg) were compared to those of d-amphetamine using an identical experimental procedure and the results are also shown in Table 2. Fenfluramine treatment led to an increased latency during all the trials but this effect was found to be statistically significant ($p<0.05$) only on the second trial. The effect on running speed, however, was marked with significant reductions occurring on all three trials. The mean running speed was only 38% that of the controls. The amount of food eaten by the rats that had received fenfluramine was extremely small, especially on the first and second trials. The increase on the third trial was almost entirely due to a single animal that had begun to eat an amount similar to that of the controls.

Experiment 3

The involvement of the serotoninergic system in food-rewarded runway behavior was further investigated by using a relatively new drug, metachlorophenylpiperazine (mCPP) which acts as a specific postsynaptic serotonin agonist and has potent anorectic activity [19]. The effects of this drug on runway performance are shown in Fig. 1. As may be seen the response was dose-dependent over a small range of concentrations. The animals receiving 0.5 mg/kg were totally unaffected and those receiving 1.0 mg/kg showed a significantly reduced performance, in latency (first trial), running speed (first and second trials) and food eaten after running (first and third trials). The highest dose (2.0 mg/kg) had a large effect on all three of these measurements in each of the trials, with a greatly increased latency, reduced running speed and less food eaten.

TABLE 2

EFFECTS OF 1.25 mg/kg d-AMPHETAMINE ON RUNWAY PERFORMANCE IN PENFLURIDOL-TREATED RATS: COMPARISON WITH 2.5 mg/kg d-FENFLURAMINE (MEAN VALUES ± SEM FOR 6 ANIMALS PER GROUP)

Pretreatment	Main treatment	Trial 1	Trial 2	Trial 3
		Inverse Latency (sec^{-1})		
Vehicle	Saline	1.38 ± 0.29	1.31 ± 0.21	1.08 ± 0.39
Vehicle	Amphetamine	1.08 ± 0.38	1.43 ± 0.35	0.50 ± 0.26
Penfluridol*	Saline	1.13 ± 0.27	1.33 ± 0.25	0.76 ± 0.16
Penfluridol	Amphetamine	1.27 ± 0.21	0.39 ± 0.17§	0.35 ± 0.09‡
—	Saline	1.13 ± 0.35	1.22 ± 0.31	0.89 ± 0.33
—	Fenfluramine	0.52 ± 0.21	0.33 ± 0.16‡	0.49 ± 0.31
		Running Velocity (m/sec)		
Vehicle	Saline	0.68 ± 0.08	0.66 ± 0.06	0.59 ± 0.11
Vehicle	Amphetamine	0.56 ± 0.05	0.54 ± 0.11	0.53 ± 0.05
Penfluridol	Saline	0.65 ± 0.05	0.71 ± 0.06	0.71 ± 0.08
Penfluridol	Amphetamine	0.57 ± 0.08	0.56 ± 0.08	0.65 ± 0.06
—	Saline	0.56 ± 0.09	0.77 ± 0.06	0.71 ± 0.08
—	Fenfluramine	0.26 ± 0.08‡	0.24 ± 0.11§	0.27 ± 0.12‡
		Food Eaten in 30 sec (g)		
Vehicle	Saline	0.38 ± 0.04	0.45 ± 0.05	0.51 ± 0.05
Vehicle	Amphetamine	0.42 ± 0.10	0.38 ± 0.08	0.42 ± 0.08
Penfluridol	Saline	0.41 ± 0.04	0.48 ± 0.05	0.46 ± 0.04
Penfluridol	Amphetamine	0.36 ± 0.04	0.39 ± 0.06	0.45 ± 0.06
—	Saline	0.35 ± 0.04	0.37 ± 0.05	0.36 ± 0.03
—	Fenfluramine	0.03 ± 0.02¶	0.02 ± 0.02¶	0.10 ± 0.10‡

*2.5 mg/kg *per os* 18 hr before first trial.

†Significantly different from the appropriate saline control on the basis of Student's *t*-test: ‡$p<0.05$; §$p<0.01$; ¶$p<0.001$.

DISCUSSION

It is commonly stated that amphetamine and fenfluramine bring about their anorectic effects in different ways. Although this is true in terms of the neurochemical pathways involved the identification of those aspects of feeding behavior that are differently affected have not yet been clarified. The present studies have attempted to focus on some specific components of feeding behavior, namely the apparent motivation for food as expressed by the runway performance of well-trained animals, and the initiation of eating after running to the food.

The preliminary experiments reported here clearly demonstrate that doses of d-amphetamine and d- fenfluramine normally found to be equianorectic act differently with respect to runway behavior. Amphetamine (1.25 mg/kg), which normally strongly suppresses the food intake of food-deprived rats, was unable to reduce runway performance significantly. However, d-fenfluramine (2.5 mg/kg), which is normally found to have the same anorectic potency as this dose of amphetamine, brought about a substantial reduction in runway performance.

Since feeding also reduces runway performance in a similar fashion this indicates that the runway is a valid experimental procedure in which to measure motivation, as it is sensitive to normal factors that influence the motivation to eat. The general locomotor behavior of the fenfluramine treated animals in the home cage appeared to be normal as were their righting and grasping reflexes. It therefore seems unlikely that runway performance was being suppressed by a reduction in the ability of the rats to run. However, at higher doses of d-fenfluramine (5 mg/kg) an obvious sedation and locomotor impairment was found in some animals and with such doses it is not appropriate to equate runway behavior with motivation for food. Accordingly these results have not been reported. Similarly with d-amphetamine at doses above 2.5 mg/kg, the appearance of stereotypy (rearing and sniffing) was found to disrupt runway behavior.

The inability of 1.25 mg/kg d-amphetamine to reduce performance could result from increased locomotor stimulation masking an underlying decrease in running times. In order to show that such a suggestion is unfounded two additional experiments were conducted. The first was indirect using diethylpropion, a drug that affects feeding through similar neurochemical pathways as amphetamine (i.e. catecholaminergic pathways) but with less stimulant properties at equivalent anorectic doses [5, 8, 21]. The second approach was more direct, eliminating the locomotor effects of amphetamine using the dopamine receptor blocking agent penfluridol [17]. Since diethylpropion, like amphetamine, had no

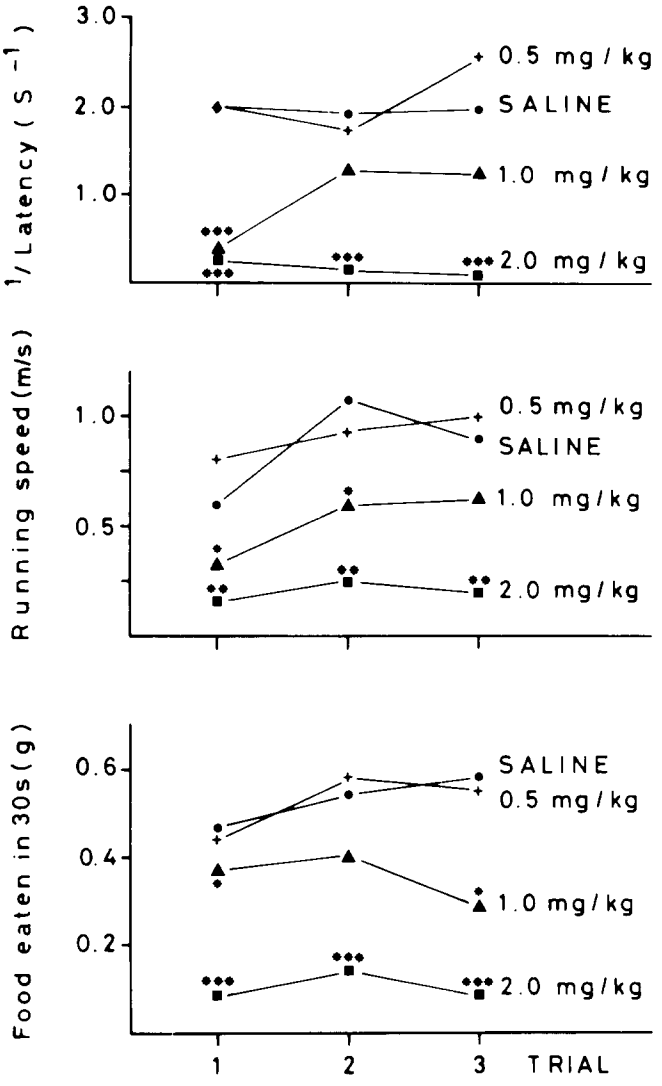

FIG. 1. The effects of mCPP on runway behavior. The drug was administered IP 40 min before the first trial and the intertrial interval was 5 min. (The statistical significance of differences from the saline treated group were assessed using Dunnett's test: $*p<0.05$; $**p<0.01$; $***p<0.001$.)

effect on runway behavior this suggests that anorectic drugs that act via catecholaminergic mechanisms appear to involve no reduction in the motivation to eat (hunger). The results with amphetamine given to penfluridol-pretreated animals also supported this contention as such animals also showed little change in running velocity or food intake. The significantly increased latency of these animals on the second and third trials, but not on the first trial, is difficult to interpret. However, it should be noted that this performance impairment is not reflected in either running velocity or feeding.

There is considerable evidence that fenfluramine exerts most of its anorectic activity through a stimulation of postsynaptic 5HT receptors, the drug having this effect by releasing serotonin from presynaptic sites and also partially blocking the reuptake mechanism [10,11]. If this is so then it may be expected that serotonin agonists will affect runway behavior in a similar way to fenfluramine. The results of the experiment with mCPP suggest that this is the case since 1.0 mg/kg mCPP, which has a similar anorectic potency as 2.5 mg/kg d-fenfluramine [19], depressed runway performance to a similar degree. However, the initiation of eating in the fenfluramine-treated animals appeared to be depressed to a greater extent than with mCPP. This may indicate that mechanisms other than 5HT receptor stimulation may be involved in the anorexia of fenfluramine.

The amount of food eaten in the 30 sec period of free access to pellets immediately after running has provided some additional evidence that 'hunger' is not affected by amphetamine but is affected by fenfluramine and mCPP. Amphetamine, either alone or in penfluridol treated animals was not only ineffective in reducing running speed but also failed to alter the amount of food eaten during each of the three 30 sec periods. This is in contrast to fenfluramine and mCPP where less food was eaten. Although a total of 90 sec for feeding is a short time it was sufficient in these experimental conditions to allow the control animals to eat about 1.5 g of food. Because there was no indication that intake was diminishing by the third trial in the amphetamine treated animals there is therefore the indication that the 'anorectic' effect of amphetamine is being overridden in the present experimental conditions. These findings parallel those for eating during tail-pinch [1], where in the course of a 10 min period the animals eat about 2 g of food. As with feeding in the runway the tail-pinch sustained eating was still able to be suppressed by fenfluramine. It is suggested that when 'activation' is at a high level, amphetamine is unable to exert its anorectic effect whereas fenfluramine is still able to reduce food intake. Under the conditions of the present experiment the animals are likely to be highly 'activated' since during training they have learnt that after running they have only a limited time in which to eat food. This therefore may prove to be an interesting feeding condition, in that it may parallel tail-pinch facilitated eating in deprived animals [1] but involving a more natural 'activation' or arousal, i.e. one that is related to the acquisition of food in a familiar situation.

The present experiments suggest that by studying food-rewarded runway behavior important behavioral distinctions may be demonstrated to occur between the 'types' of anorexia induced by various drugs. The technique has clearly dissociated the effects of two catecholaminergic agents, d-amphetamine and diethylpropion from the effects of two serotoninergic treatments, d-fenfluramine and mCPP. Further studies are currently in progress in which runway performance and subsequent feeding are observed until the onset of satiety in control animals. We believe that this technique may prove to be a valuable tool in studying the mode of action of drugs that affect feeding behavior.

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