Pharmacology Biochemistry & Behavior, Vol. 32, pp. 1025–1031. © Maxwell Pergamon Macmillan plc, 1989. Printed in the U.S.A. 0091-3057/89 $3.00 + .00

Effects of Dexfenfluramine on the Feeding Behavior of Rats Foraging in the Cold for Palatable Bait

MICHEL CABANAC,* CHANTAL FERBER† AND MARC FANTINO‡

*Université Laval, Faculté de Médecine, Ste-Foy, Québec, G1K 7P4, Canada
†Université Claude Bernard, Faculté de Médecine Lyon-Sud, F 69600 Oullins Cedex, France
‡Université de Bourgogne, Faculté de Médecine de Dijon
7, Boulevard Jeanne d'Arc, F 21033 Dijon Cedex, France

Received 6 November 1987

CABANAC, M., C. FERBER AND M. FANTINO. *Effects of dexfenfluramine on the feeding behavior of rats foraging in the cold for palatable bait.* PHARMACOL BIOCHEM BEHAV **32**(4) 1025–1031, 1989.—An alimentary/thermic conflict of motivation was used to explore the effects of very low doses of dexfenfluramine (dFF), an anorectic serotoninergic agonist, on the parameters of food motivation, drive and incentive (or palatability). Six rats trained to feed 2 hr/day, were given the possibility to feed on chow in a shelter (25°C), and to get a snack of shortcake, a highly palatable bait, from a feeder placed 16 m away in a very cold environment (−15°C). dFF at 0.6 or 1.25 mg/kg decreased neither the chow intake in the shelter, nor the mean duration of the snacks in the cold, which is the parameter believed to be the best indicator of incentive. In contrast, dFF reduced the number of trips to the bait in the cold as well as the total mass of palatable bait ingested and the mean amount ingested by snack. Such an effect was no longer observed after a food restriction had reduced the body weight of the rats to 90% of its initial value. It is concluded that, even at doses too small to reduce the consumption of basic food, dFF decreases the drive to get palatable food.

Dexfenfluramine Conflict Food motivation Drive Incentive Cold Palatability Set-point Body weight

PROGRESS in obesity therapy requires development of new drugs with leptogenic activity (31). Fenfluramine and especially its racemic component dexfenfluramine (dFF) are such medications which reduce body weight by acting on both sides of the energy balance: increase of energy expenditure (12, 35, 39) and decrease of energy intake (4,15). It has been established that the anorexigenic effect of dFF expresses a reduction of the motivation to get and to ingest food (42). According to Hull (22) the motivation to eat results from the interaction of two variables: the *drive* which is correlated to the internal energetic needs, and the *incentive* which is related to the sensory rewarding properties of food, i.e., to the *palatability*. This raises the question as to whether dFF reduces the motivation to eat by decreasing the drive or the incentive. There are experimental arguments for both hypotheses.

It is obvious that dFF would reduce the drive to search for and ingest food if it reduces energy needs as a consequence of a hypothetical decrease of the body weight set-point it induces. Such an effect has been suggested by Stunkard from clinical observations (36,37), then demonstrated in animals from experimental measurements of the rat's food hoarding behavior (16,17). The alternative hypothesis, that dFF reduces the incentive associated to food, may be put forward from the observation that dFF selectively decreases the intake of carbohydrates and sweet food (6, 10, 21, 48). However, this second hypothesis requires further evidence from studies in animals as well as in humans.

The present work was undertaken to explore further the action of dFF on food intake, and especially the hypothesis that dFF decreases the pleasantness of palatable foods. To judge it, we used the obstruction principle of Warden (44) improved for this very purpose (8,24). The method is based on a conflict of motivation between food and temperature. It consists of giving rats a shelter with food and water ad lib in a very cold environment. The palatable bait tested is placed in the cold environment 16 m away. Thus, the pleasantness of the bait is pitted against the aversiveness of the cold environment. One advantage of this method is that it allows an estimation of the animal's perception of food palatability independent from the amount of bait eaten. In addition, it is possible to estimate the drive to feed from the number of trips in the cold and from the amount eaten. Finally, in such a situation, rats eat once a day, which is convenient with short-lived drugs. An injection, prior to the beginning of the session, places the animal under the influence of the drug for the whole session. Low doses

[1]Requests for reprints should be addressed to Professor Marc Fantino.

of dFF were used in order to minimize any possible side effects.

METHOD

Animals and Rearing Conditions

Six male rats were housed individually and trained to feed two hours per day (12:00 to 14:00 hr) in the animal quarters for several weeks including weekends. At feeding time, they received regular laboratory chow ad lib. Water was present in their cages at all times. Food intake and body mass (b.wt.) were weighed five days per week. Ambient temperature in the animal quarters was 21°C (range: 19–23°C). The experiments started when the rats were thoroughly trained to the experimental apparatus.

The time and duration of the experimental sessions were the same as those of the usual meals in the animals' quarters.

Experimental Apparatus

A complete description of the apparatus will be found elsewhere (25). Once a week, each rat was transported between 12:00 and 14:00 hr in the experimental apparatus mainly composed of zigzag alley 16 m long. At one of the extremities of the alley, each rat in turn found its own warm shelter with water and laboratory chow. At the other extremity, a feeder contained palatable shortcake, in powder form to prevent hoarding. The alley and the feeder were in a climatic chamber at −15°C whereas the shelter was heated with an infrared bulb to +25°C.

Thus, the rats could feed on laboratory chow in the shelter and venture into the cold environment to obtain palatable food (= snack). In control sessions, the feeder in the cold contained powdered chow. Electric contacts permitted the recording of every passage of the rat through its shelter/door, and the rat's presence at the feeder in the cold.

Measurements

The food ingested in the warm shelter and from the cold feeder was measured by weighing. The number of trips to the feeder and the total time spent at the feeder were directly recorded from the electric contacts placed at each extremity of the alley. Mean snack duration and caloric intake were computed from the measured values. When several snacks occurred in a session, all the data were computed as a mean for each rat during that session. Then the results were computed as group means. All the recorded variables being parametric, Student's *t*-test (paired when applicable) and Duncan multiple range test, analysis of variance, were used to compare the group means. The Duncan analysis of variance was conducted at the probability level of $p<0.05$ and the results are plotted on Figs. 1 to 5.

Drug and Controls

One hour prior to the beginning of experimental sessions, the rat received an intraperitoneal (IP) injection of either dFF 0.6 mg/kg, or dFF 1.25 mg/kg, or the vehicle (isotonic saline). According to the pharmacokinetics of dFF and nordexfenfluramine, its main active metabolic derivative (9, 20, 33), a delay of one hour was judged acceptable to run the sessions during the peak activity of the drug. The rats were exposed to six conditions by combining two baits found in the cold, and three IP injections. Each rat was, therefore, its own control. The six conditions were permuted in individual rats so as to suppress, in the group, any possible effect of the sequence.

EXPERIMENT 1

The aim of this experiment was to check whether the dFF would decrease the rewarding properties of shortcake, a bait found quite attractive in other experiments (8, 24, 25). The palatability of the shortcake was judged from the mean duration of time tolerated by the rats eating the bait in the cold. The rats received no treatment other than IP injections of saline or dFF as described above in the Method section.

TABLE 1

MASSES OF FOOD INGESTED BY THE RATS

	(A) Chow Ingested At Home (g)		
		Dexfenfluramine (mg/kg)	
	Saline	0.6	1.25
With chow bait at feeder	18.4 ± 1.6*	14.9 ± 1.9	13.5 ± 3.0
with Shortcake bait at feeder	15.1 ± 1.8	11.5 ± 1.8†	11.2 ± 1.5†
	(B) Bait Ingested at Feeder (g)		
		Dexfenfluramine (mg/kg)	
	Saline	0.6	1.25
With chow bait at feeder	1.6 ± 0.4	0.7 ± 0.3	0.03 ± 0.03
with Shortcake bait at feeder	18.6 ± 1.5‡	12.5 ± 2.0‡	4.8 ± 3.1

Mean mass (g) of chow ingested in the shelter (A), and mean mass (g) of bait ingested from the feeder in the cold enviornment (B), during the 2-hr experimental sessions according to the nature of the injection and the nature of the bait in the cold. All figures are statistically identical but for * which is different from boxes †, and for ‡ which are different from each other and from all other boxes (Duncan multiple range test, analysis of variance: $p<0.05$).

RESULTS

Chow Ingested in the Shelter

Comparing the amount of energy ingested under identical pharmacological conditions, after either saline or dFF, it can be noted in Table 1 (part A) and Fig. 1 that, when shortcake was available in the cold instead of chow, the decrease of chow consumption in the shelter was slight (nonsignificant) and insufficient to compensate for the large amount of palatable bait ingested at the cold feeder. It can also be noted that, when chow was available at the feeder, the amount of chow eaten by the rats in the shelter was approximately the same after dFF as after saline (slight but nonsignificant decrease). Finally, the difference in chow ingested in the shelter reached the level of statistical significance only when shortcake was combined with dFF.

Behavior During Control Sessions

After saline injections the rats snacked the same number of times, regardless of the bait in the feeder, in the cold environment (Fig. 2). In contrast, the mean duration of snacks in the cold (Fig. 3), and the total snacks duration (Fig. 4) were significantly longer with shortcake (paired *t*-tests: $p<0.05$ and $p<0.01$). The longer stays in the cold environment resulted in a shortcake ingestion significantly greater than chow ingestion (Table 1, Figs. 1 and 5).

Effect of dFF

The higher dose of dFF (1.25 mg/kg) significantly reduced the

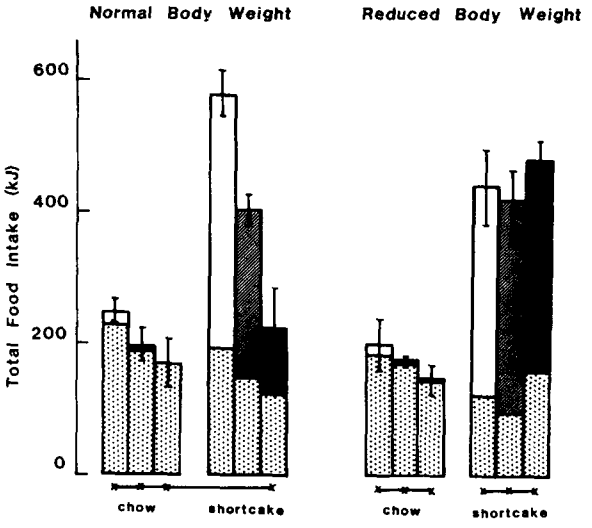

FIG. 1. Mean (±S.E.M.) amount of energy eaten in the shelter (dotted columns) and at the cold feeder after the rats had received either saline 1 ml/kg (open columns), or dFF 0.65 mg/kg (hatched columns), or dFF 1.25 mg/kg (black columns). The type of bait in the cold indicated below the columns. Left: rats at normal body weight (fed 2 hr/day). Right: rats with body weight reduced to 90% of normal body weight. In each group, means not underlined by a same line (X—X) are significantly different (Duncan multiple range test, analysis of variance $p<0.05$).

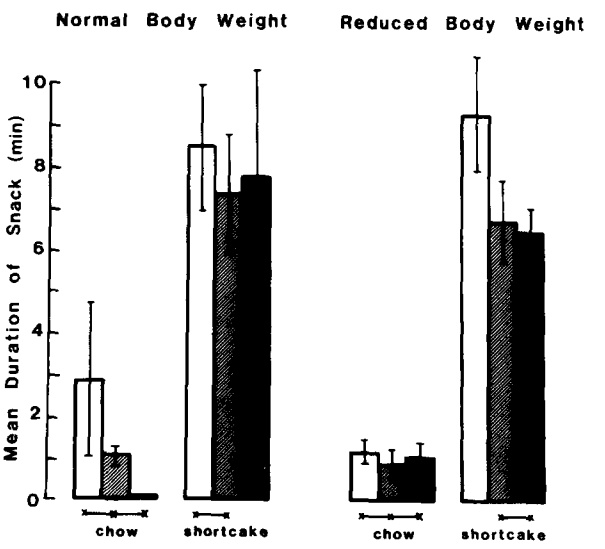

FIG. 3. Mean (±S.E.M.) duration of rat snacks at the cold feeder after the rats had received saline 1 ml/kg (open columns), or dFF 0.65 mg/kg (hatched columns), or dFF 1.25 mg/kg (black columns). The type of bait in the cold is indicated below the columns. Left: rats at normal body weight (fed 2 hr/day). Right: rats with body weight reduced to 90% of normal body weight. In each group, means not underlined by a same line (X—X) are significantly different (Duncan multiple range test, analysis of variance, $p<0.05$).

number of trips to the bait (Fig. 2) and this number was then not significantly different when the bait was palatable (shortcake) or not (chow). Several rats did not leave the shelter at all during these sessions. The lower dose had no effect on this parameter.

Although the meals were less frequent after dFF 1.25 mg/kg, once the rats had reached the cold feeder, they spent a similar amount of time eating shortcake. Indeed, the mean duration of shortcake-snacks (Fig. 3) was apparently not influenced by dFF even after the 1.25 mg/kg dose. However, Fig. 5 shows that the rats ingested a lower mass of bait per snack after they had received dFF and the difference was significant when the bait was shortcake. With shortcake as bait, and after dFF 1.25 mg/kg or 0.6 mg/kg, both the decreased number of snacks (Fig. 2) and the decrease of the mean mass of the bait ingested per snack (Fig. 5) resulted in a decrease of the total energy intake in the cold environment (Fig. 1). This effect already noticeable with dFF 0.6 mg/kg reached the threshold of statistical significance for the three parameters under dFF 1.25 mg/kg. Finally, the reduced number of snacks after dFF 1.25 mg/kg resulted in a decrease of the total snack duration (Fig. 4).

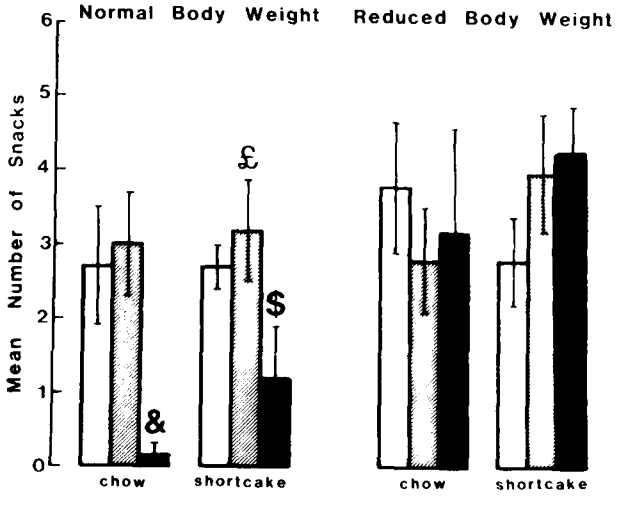

FIG. 2. Mean (±S.E.M.) number of snacks made by the rats at the cold feeder after the rats had received saline 1 ml/kg (open columns), or dFF 0.65 mg/kg (hatched columns), or dFF 1.25 mg/kg (black columns). The type of bait is indicated below the columns. Left: rats at normal body weight (fed 2 hr/day); Column & different from all other but $; Column $ not different from all other but £ and &. Right: rats with body weight reduced to 90% of normal body weight. All columns are not significantly different.

DISCUSSION

It has been demonstrated that the two-hour feeding schedule produces intense thermogenesis in the rats at the time of the meal (38). In addition, racemic fenfluramine has been shown to raise postingestive thermogenesis (29). In our experiment, both effects should therefore enhance the rats' foraging behavior in the cold. Actually, the rats remained in their shelter when they were under dFF.

dFF had very little effect on the consumption of chow in the shelter, regardless of the dose. The drugs' absent influence resulted from the low doses used in this experiment in order to limit the anorexigenic effects in the 2/hr day feeding-protocol used (20, 27, 33). In contrast, the effect of dFF was obvious on the consumption of the food, whether or not palatable, from the feeder in the cold environment. dFF reduced the number of trips to the cold, that we consider as reflecting the eagerness to get and ingest the food (8,25). A possible explanation could be that the drug

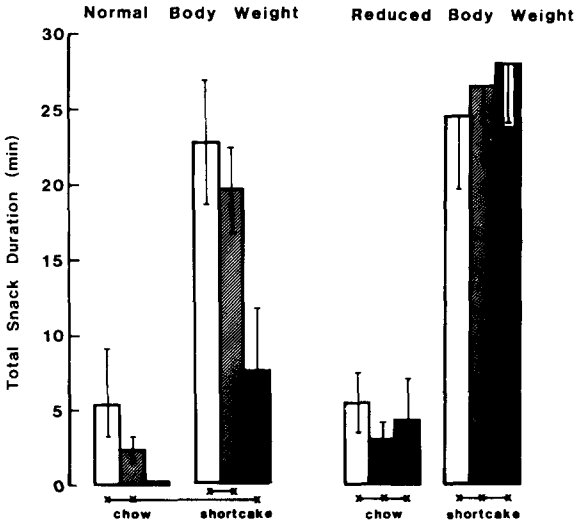

FIG. 4. Mean (±S.E.M.) total snack duration at the cold feeder after the rats had received saline 1 ml/kg (open columns), or dFF 0.65 mg/kg (hatched columns),or dFF 1.25 mg/kg (black columns). The type of bait in the cold is indicated below the columns. Left: rats at normal body weight (fed 2 hr/day). Right: rats with reduced body weight to 90% of normal body weight. In each group, means not underlined by a same line (X—X) are significantly different (Duncan multiple range test, analysis of variance, $p<0.05$).

rendered the bait less palatable but the maintained duration of snacks would not support this hypothesis. Another possible explanation could be found in drowsiness or decrease of motor capacity. The very low doses used run contrary to this hypothesis

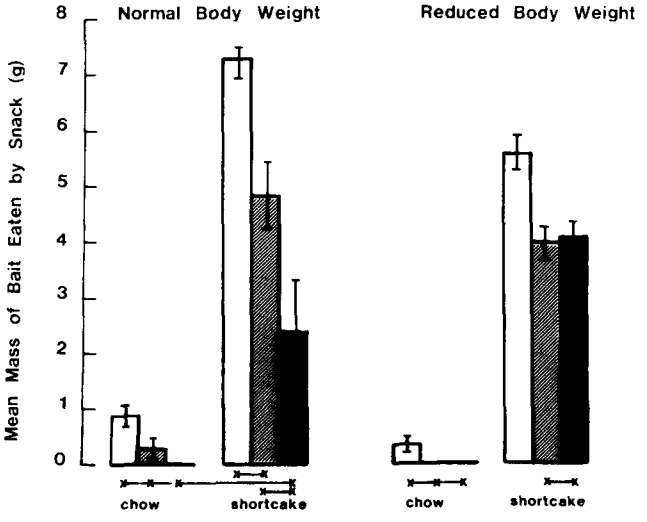

FIG. 5. Mean (±S.E.M.) mass of bait eaten per snack at the cold feeder after the rats had received saline 1 ml/kg (open columns), or dFF 0.65 mg/kg (hatched columns), or dFF 1.25 mg/kg (black columns). The type of bait in the cold is indicated below the columns. Left: rats at normal body weight (fed 2 hr/day). Right: rats with reduced body weight to 90% of normal body weight. In each group, means not underlined by a same line (X—X) are significantly different (Duncan multiple range test, analysis of variance, $p<0.05$).

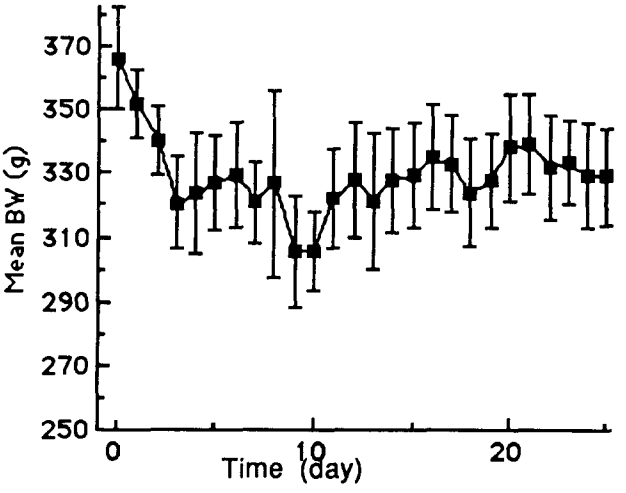

FIG. 6. Mean (±S.E.M.) body weight of the rats during the course of Experiment II. Day zero was the last of Experiment I.

which cannot be totally discarded at this point, though. Finally, it can be hypothesized that dFF had decreased the rats' drive to forage for food, an effect that was perhaps minimized by the thermogenic effect of the drug. As a result of the lower number of snacks the total amount of palatable bait ingested in the cold was significantly decreased after 0.6 mg/kg and further after 1.25 mg/kg. At this dose dFF restored total amount of shortcake ingested, total snack duration, as well as a mean mass of bait ingested by snack to values similar to those observed when the chow bait was available. The results can be summarized by stating that the drug rendered shortcake, no more attractive than chow. Since the amount of chow eaten in the shelter was not clearly decreased, very low doses of dFF spared the consumption of basic food. Such interpretation would conform to Wurtman *et al.*'s hypothesis in which low doses of dFF selectively suppress craving for palatable foods (47,48), but spare protein consumption (21,46).

If the mean duration of snacks in the cold provides a measure of the palatability of food at the feeder (since the rat leaves the feeder when the aversiveness of the cold environment has become stronger than the pleasantness of the bait), then the results indicate that the dFF did not reduce the palatability of shortcake in rats with normal body weight, (since the mean snack duration was not influenced by dFF). It is therefore likely that, once such food was made available, dFF at low doses did not modify the incentive of the palatable food.

EXPERIMENT II

Experiment I demonstrated that low doses of dFF did not render the rats anorexigenic but reduced the number of their foraging trips to food without reducing the palatability of the bait. Experiment II was undertaken to check whether this effect was body weight dependent. (This experimentation was suggested by Dr. S. Nicolaidis who predicted the results accurately.) The six rats of the initial group were placed on a limited food intake schedule until their body weight was reduced to about 90% of the value observed during the previous weeks. Such a decrease in body weight was expected to be larger than any hypothetical lowering of body weight set-point due to the small doses of dFF in this experiment. The hypothesis was that, if the effect of dFF consists in lowering of the set-point b.wt. as previously proposed

(16, 17, 36, 37), all effects of dFF would disappear in deprived rats. Experiment II was therefore the exact replication of Experiment I except for the reduced body weight. The rats' body weight was maintained stable, over the six weeks of Experiment II, by weighing the rats every day and providing them with a monitored amount of chow on days when they were not under experiment. The mean body weight is shown in Fig. 6.

RESULTS AND DISCUSSION

The total amount of food ingested by the rats was slightly lower during the control session of Experiment II than during control session of Experiment I (Fig. 1). Figures 1, 2, 3, 4 and 5 show that dFF had lost its effect in these food-deprived animals. The only noticeable difference between treated and control rats was in mean meal duration (Fig. 3) which, although high, was lower in treated rats than in the nontreated, resulting in a lower mass of shortcake ingested per snack (Fig. 5). The difference was significant only after dFF 1.25 mg/kg. The reduction, by dFF, of the drive to forage in the cold observed in Experiment I, disappeared in the rats after body weight reduction. Such a result rules out any influence of the drug on the rats motricity or level of vigilance but is compatible with the hypothesis of a reduction of body weight set-point by the drug, as suggested by Levitsky *et al.* (30) from animal experiments, or Stunkard *et al.* (36,37) from clinical observations in humans, an hypothesis which was confirmed by Fantino *et al.* (16,17) from the observation of the rat's food-hoarding response. Thus, the drug did not lose its activity but the action was simply masked by the large decrease in body weight created in the rats by the experimenters.

The small but significant reduction in mean shortcake meal duration in the cold environment would indicate that the drug reduced the palatability of shortcake in rats whose body weight was maintained at 90% of its normal level. This result is difficult to reconcile with the maintained palatability in Experiment I. However, it should be pointed out that even if (marginally) statistically significant, the decrease was relatively small and other results may have been obtained with larger groups of rats. Indeed the palatability of shortcake remained high when compared with that of chow.

GENERAL DISCUSSION

CRITERIA OF MOTIVATION

Preference for a food or flavor is usually judged from the amount eaten (42,45). However, it is recognized that in humans (2) and even more so in animals (11), this is an imperfect index of the real drive to feed. Such a technique has been shown to be particularly unsuitable to evaluate the palatability of the food (3). Preference tests are often used but they only allow a ranking of foods according to their palatability. An alternative or a complementary method, to judge motivation to eat, is the measurement of the animals' performances in a food rewarding runway (26, 40, 42). Using such a method, Kirkham and Blundell (26) have shown that dFF (1.5 mg/kg) hastens the onset of satiation. It is worth noting that the present results are in accordance with this finding. However, the motivational conflict used in this work has the advantage of allowing evaluation of incentive, in addition to drive to feed. Mean meal duration should reflect palatability, since meal duration reflects the time when the constant environmental temperature was judged by the rat to be more aversive than the attraction for the bait, and the bait attractiveness depends on its palatability (8,25). The robustness of this method was confirmed in control sessions by the long duration of meals in the cold with a palatable bait. However, this technique has the disadvantage of a possible interference with thermogenic effects of the drug tested rendering the rats more tolerant of the cold environment. Indeed, dFF increases the thermogenesis induced by food (29) and by exercise (12). So it is possible that a minor reduction of the shortcake palatability by dFF in the ad lib fed rats (Experiment I) has been masked, to some degree, by the drug-induced thermogenesis. Since body weight loss reduces thermogenesis (1,23) it is also possible that the food-related thermogenesis was suppressed in the food-restricted rats (Experiment II) uncovering the small (but significant) reduction of palatability observed with dFF in Experiment II.

SET-POINT, PALATABILITY AND dFF

In rats with low body weight, the disappearance of the drug's effects is in accordance with the hypothesis that the main effect of dFF is to decrease the body weight set-point (7, 17, 29, 36, 37). According to this hypothesis, the drug made the subjects regulate their body weight (or fat mass) at a lower level,thus reducing their energy needs. Such an effect can be inferred from the observation that any possible drug effect on the rats disappeared after they had been food-deprived and had lost weight (Experiment II). The alternative to this hypothesis would be that the drug failed to affect intake when body weight was reduced by 10% simply because the animals were so hungry that the drug effect was overridden or the test situation insensitive. However, this alternative is ruled out by the fact that the action of the drug was visible only on palatable diet. If the rats had been ravenously hungry when deprived they would have shown it by increasing their intake of chow above the amount eaten in Experiment I; this was not the case.

The absence, or only minor, effect of dFF on the incentive parameter of food motivation may explain an otherwise uninterpretable observation by Blundell and Hill (5): dFF did not induce any change in the affective response for sweet gustatory stimuli in obese subjects. The absence of dFF effect on the sensorial rewarding properties of food is in contrast with the strong activity on this parameter of other anorexic drugs, such as the opioid receptor antagonists, naloxone or naltrexone (18,19). Thus, different drugs may have anorexic activities which involve different mechanisms.

EFFICACIOUS DOSE OF dFF

The most striking point of the present study is that small doses of dFF, insufficient to induce significant anorexia toward basic food, reduced the drive to forage outside even when the bait was palatable. These results corroborate previous observations by Hirsh *et al.* (21) who found that, in juvenile rats maintained on a 8-hour/day feeding schedule 4 mg/kg of dFF were required to reduce the consumption of basic diet by 50%, whereas at a lower dose of 1.25 mg/kg, only the intake of a carbohydrate rich diet was reduced (by about 40%). It is unlikely that, in the present work, the reduction of the number of trips to the feeder in the cold came from an unspecific decrease of locomotor activity by dFF since the drug did not change this parameter in the deprived rats (Experiment II). Thus, dFF seems to be more active on parameters which reflect the motivation to eat, rather than on food consumption itself as previously underlined by Rolland (32).

In a recent review Rowland and Carlton (34) have pointed out that the dose of dFF capable of suppressing 50% of the food intake, or specific behaviors related to food motivation (D1 50) ranges between 0.6 and 1.25 mg/kg according to experimental protocol used. For example, doses as low as 0.63 mg/kg decreased both starting and running speed in a food-rewarded runway (40). With the thermic/alimentary conflict of motivation used here, the

efficacious dose was quite close to such a value since the effect of dFF was noticeable with the 0.65 mg/kg dose, and was significant at 1.25 mg/kg. It is worth noting that other behaviors are even more sensitive to dFF. For example, Fantino *et al.* (13) have observed that 0.3 mg/kg of dFF suppressed 85% of food hoarding by rats, two hours after IP injection, and that eight hours later the inhibition was still important (40%). Leibowitz *et al.* (28) reported that peripheral injection of 0.06–0.25 mg/kg, at the start of the dark cycle, preferentially suppressed carbohydrate intake, whereas higher doses (0.5–2.0 mg/kg) reduced protein and fat intake as well as carbohydrate. Finally, it appears that in rats, dFF may act on the control of food intake at doses ranging from ten to twenty times lower than doses previously proposed to induce body weight loss (15, 17, 30).

ACKNOWLEDGEMENTS

This work was supported by grants provided by the Université de Dijon (France), Laboratoires Servier (France), I.N.S.E.R.M. (Contrat libre 85-7006) and C.N.R.S. (RCP 819). We thank P. Noirot and E. Dominiak for their excellent technical and secretarial assistance.

REFERENCES

1. Apfelbaum, M.; Bostaron, J.; Lacatis, D. Effect of caloric restriction and excessive caloric intake on energy expenditure. Am. J. Clin. Nutr. 24:1405–1409; 1971.
2. Bellisle, F.; Le Magnen, J. The analysis of human feeding patterns. Appetite 1:141–150; 1980.
3. Berridge, K. C.; Grill, H. J. Isohedonic tastes support a two-dimensional hypothesis of palatability. Appetite 5:221–231; 1984.
4. Blundell, J. Serotonin and appetite. Neuropharmacology 23:1537–1551; 1984.
5. Blundell, J. E.; Hill, A. J. On the mechanism of action of dexfenfluramine: effect on alliethesia and appetite motivation in lean and obese subjects. Clin. Neuropharmacol. 11:S121–S134; 1988.
6. Borsini, F.; Bendotti, C.; Samanin, R. Salbutamol, d-amphetamine and d-fenfluramine reduce sucrose intake in freely fed rats by acting on different neurochemical mechanisms. Int. J. Obes. 9:277–283; 1985.
7. Brindley, D. N.; Saxton, J.; Shahidullah, H.; Armstrong, M. Possible relationships between changes in body weight set-point and stress metabolism after treating rats chronically with d-fenfluramine. Effects of feeding rats acutely with fructose on the metabolism of corticosterone, glucose, fatty acids, glycerol and triacylglycerol. Biochem. Pharmacol. 34:1265–1271; 1985.
8. Cabanac, M.; Johnson, K. G. Analysis of a conflict between palatability and cold exposure in rats. Physiol. Behav. 31:249–253; 1983.
9. Caccia, S.; Ballabio, M.; Guiso, G.; Rocchetti, M.; Garattini, S. Species differences in the kinetics and metabolism of fenfluramine isomers. Arch. Int. Pharmacodyn. 258:15–28; 1982.
10. Cooper, S. J.; Neill, J. 5-HT receptors and the sweet tooth. Trends Pharmacol. Sci. 8:199–200; 1987.
11. Di Battista, D.; Bédard, M. Effects of food deprivation on hunger motivation in golden hamsters (*Mesocricetus auratus*). J. Comp. Psychol. 101:183–189; 1987.
12. Even, P.; Nicolaidis, S. Dextrofenfluramine increases energy cost of muscular effort. Pharmacol. Biochem. Behav. 24:647–655; 1986.
13. Fantino, M.; Boucher, H.; Faion, F.; Mathiot, P. Dexfenfluramine and body weight regulation: Experimental study with hoarding behavior. Clin. Neuropharmacol.11:S97–S104; 1988.
14. Fantino, M.; Cabanac, M. Body weight regulation with a proportional hoarding response in the rat. Physiol. Behav. 24:939–942; 1987.
15. Fantino, M.; Faion, F. Lowering body weight set-point by dextrofenfluramine. In: Vague, J.; Bjorntorp, P.; Guy-Grand, B.; Rebuffe-Scrive, M.; Vague, P., eds. Metabolic complications of humans obesities. Amsterdam: Excerpta Medica; 1985:185–197.
16. Fantino, M.; Faion, F. Dextrofenfluramine and body weight regulation. In: Bender, A. E.; Brookes, L. J., eds. Human body weight. London: Pitman; 1987:247–254.,
17. Fantino, M.; Faion, F.; Rolland, Y. Effect of dexfenfluramine on body weight set-point: study in the rat with hoarding behaviour. Appetite 7:115–126; 1986.
18. Fantino, M.; Hosotte, J.; Apfelbaum, M. An opioid antagonist, naltrexone reduces the preference for sucrose in man. Am. J. Physiol. 251:R91–R96; 1986.
19. Fantino, M.; Rossetti,Y.; Cabanac, M. Dextrofenfluramine, palatability and conflictual motivation. In: Ferrari, E.; Brambilla, F., eds. Disorders of eating behaviour: A psychoneuroendocrine approach. Oxford: Pergamon Press; 1985:375.
20. Garattini, S.; Caccia, S.; Mennini, T.; Samanin,R.; Consolo, S.; Ladinski, H. Biochemical pharmacology of the anorexic drug fenfluramine: a review. Curr. Med. Res. Opin. 6:15–27; 1979.
21. Hirsch, J. A.; Goldberg, S.; Wurtman, R. J. Effects of (+) or (−) enantiomeres of fenfluramine or norfenfluramine on nutrient selection by the rats. J. Pharm. Pharmacol. 34:18–21; 1982.
22. Hull, C. L. Principles of behavior. New York: Appleton-Century-Crofts; 1943.
23. Jequier, E. Thermogénése induitepar les aliments chez l'homme: Son rôle dans la régulation pondérale. J. Physiol. (Paris) 80:129–140; 1985.
24. Johnson, K. G.; Cabanac, M. Homeostatic competition between food intake and temperature regulation in rats. Physiol. Behav. 28:675–679; 1982.
25. Johnson, K. G.; Cabanac, M. Homeostatic competition in rats fed at varying distances from a thermoneutral refuge. Physiol. Behav. 29:715–720; 1982.
26. Kirkham, T. C.; Blundell, J. E. Effect of naloxone and naltrexone on the development of satiation measured in the runway: Comparisons with d-amphetamine and d-fenfluramine. Pharmacol. Biochem. Behav. 25:123–128; 1986.
27. Le Douarec, J. C.; Schmitt, M.; Laubie, M. Etude pharmacologique de la fenfluramine et de ses isoméres optiques. Arch. Int. Pharmacodyn. 161:205–232; 1966.
28. Leibowitz, S. F.; Weiss, G. F.; Shor-Posner, G. Hypothalamic serotonin: Pharmacological, biochemical and behavioral analyses of its feeding-suppressive action. Clin. Neuropharmacol. 11:S51–S71; 1988.
29. Levitsky, D. A.; Schuster, J. A.; Stallone, D.; Strupp, B. J. Modulation of the thermic effect of food by fenfluramine. Int. J. Obes. 10:169–173; 1986.
30. Levitsky, D. A.; Strupp, B. J.; Lupoli, J. Tolerance to anorectic drugs: Pharmacological or artifactual. Pharmacol. Biochem. Behav. 14:661–667; 1981.
31. Nicolaidis, S.; Even, P. Metabolic action of leptogenic (anorexigenic) agents on feeding and body weight. In: Carruba, M. O.; Blundell, J. E., eds. Pharmacol. of eating disorders: Theoretical and clinical developments. New York: Raven Press; 1986:131–177.
32. Rolland, Y. Mechanisms of action of dexfenfluramine. Is there a possibility for an integrative approach? In: Ferrari, E.; Brambilla, F., eds. Disorders of eating behaviour: A psychoneuroendocrine approach. Oxford: Pergamon Press; 1986:391–401.
33. Rowland, N. E.; Carlton, J. Neurobiology of an anorectic drug: Fenfluramine. Prog. Neurobiol. 27:133–162; 1986.
34. Rowland, N. E.; Carlton, J. Dexfenfluramine: Effects on food intake in various animal models. Clin. Neuropharmacol. 11:S33–S50; 1988.
35. Schuster, J. A.; Lewvitsky, D. A. Modulation of the thermogenic effects of nutrients by fenfluramine. Fed. Proc. 41:3926; 1982.
36. Stunkard, A. J. Minireview: Anorexic agents lower a body weight set-point. Life Sci. 30:2043–2055; 1982.
37. Stunkard, A. J. Regulation of body weight and its implications for the treatment of obesity. In: Carruba, M. O.; Blundell, J. E. Pharmacology of eating disorders: Theoretical and clinical developments. New York: Raven Press; 1986:101–116.
38. Sugano, Y.; Nagasaka, T. Effects of diurnal two-hour feeding on heat balance in rats. In: Hales, J. R. S., ed. Thermal physiology. New York: Raven Press; 1984; 165–168.
39. Tagliafero, A. R.; Robert, J. S.; Davis, J. R. Effect of fenfluramine on food intake, body temperature and energy metabolism in adult rat. Fed. Proc. 41:3933; 1982.

40. Thurlby, P. L.; Garattini, S.; Samanin, R. Effects of serotonin antagonists on the performance of a simple food acquisition task in rats treated with fenfluramine isomers. Pharmacol. Res. Commun. 17:1129–1139; 1985.
41. Thurlby, P. L.; Grimm, V. E.; Samanin, R. Feeding and satiation observed in the runway: The effects of d-amphetamine and d-fenfluramine compared. Pharmacol. Biochem. Behav. 18:841–846; 1983.
42. Thurlby, P. L.; Samanin, R. Effects of anorectic drugs and prior feeding on food-rewarded runway behavior. Pharmacol. Biochem. Behav. 14:799–804; 1981.
43. Vasquez, M.; Pearson, P. B.; Beauchamp, K. G. Flavor preference in malnourished Mexican infants. Physiol. Behav. 28:513–519; 1982.
44. Warden, C. J. Animal motivation experimental studies on the albino rat. New York: Columbia University Press; 1931.
45. Wene, G.; Barnwell, M.; Michell, D. S. Flavor preference, food intake and weight gain in baboon. Physiol. Behav. 28:569–773; 1982.
46. Wurtman, J.; Wurtman, R. Fenfluramine and fluoxetine spare protein consumption while suppressing caloric intake by rats. Science 198: 1178–1180; 1979.
47. Wurtman, J.; Wurtman, R. Drugs that enhance central serotoninergic transmission diminish selective carbohydrate consumption by rats. Life Sci. 24:895–904; 1979.
48. Wurtman, J.; Wurtman, R.; Mark, S.; Tsay, R.; Gilbert, W.; Growdon, J. D-fenfluramine selectively suppresses carbohydrate snacking by obese subjects. Int. J. Eat. Disord. 4:89–99; 1985.