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Do Serotoninergic Drugs Decrease Energy Intake by Reducing Fat or Carbohydrate Intake? Effect of d-Fenfluramine With Supplemented Weight-Increasing Diets

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BLUNDELL, J. E. AND A. J. HILL. *Do serotoninergic drugs decrease energy intake by reducing fat or carbohydrate intake? Effect of d-fenfluramine with supplemented weight-increasing diets.* PHARMACOL BIOCHEM BEHAV **31**(4) 773–778, 1988.—The capacity of serotoninergic drugs to selectively suppress carbohydrate (CHO) intake was investigated using a procedure sensitive to drug action. The drug d-fenfluramine was administered chronically to rats whose weight had been increased by exposure to either a fat or CHO-supplemented hyperphagia-inducing diet. The drug exerted a more potent anorexic effect and weight-reducing action in rats given the dietary supplements than in control chow-fed rats. Tolerance to the drug was not apparent even after 40 days of treatment. However, there was no evidence for a selective inhibition of CHO intake, nor was the drug more potent with the CHO-supplemented diet. d-Fenfluramine was equally effective against the hyperphagia and weight gain induced by either fat or CHO supplements.

d-Fenfluramine Serotonin Carbohydrate Fat Diet-induced hyperphagia Tolerance

IT is well known that experimental manipulations of serotonin (5-HT) metabolism give rise to pronounced changes in food consumption and feeding (3,5). In turn, these data suggest a possible role (or roles) for 5-HT in the regulation of energy balance or nutrient intake. More specifically, it has been proposed that a feedback loop exists which links dietary composition (balance of protein and carbohydrate) to plasma profiles of amino acids, which in turn influences brain uptake of neurotransmitter precursors and finally neurotransmitter agents determine behavior [e.g., (1, 14, 15, 24)]. The most prominent versions of this idea suggest that 5-HT is involved in long-term regulation of protein intake or short-term control of carbohydrate intake. Both hypotheses predict changes in the intake of the ratio of protein:carbohydrate following experimental treatments by 5-HT agents. This feature of the hypotheses has been subjected to criticism and comment (9,13). The end-stage of the physiological loop has been the target of various experimental approaches which generally involve pharmacological treatment by 5-HT agents in conjunction with the monitoring of food intake in animals offered a choice of diets varying in nutrient composition.

There has been a variable outcome to experiments using this strategy. Some reports indicate either a 'protein-sparing' (18,35) or a 'carbohydrate suppressive' (28,36) action of agents such as fenfluramine, fluoxetine, MK-212, or quipazine whose ultimate action is believed to be an activation of central (and peripheral) 5-HT receptors. Other studies have reported a mild action of such agents (25) whose action depends on a number of variables including the nature of the diet offered (4,26). It has also been reported that tryptophan adjusts protein/carbohydrate selection (24) although negative findings have also appeared (31). Interestingly, certain studies have revealed a modulating effect of dl-fenfluramine (30) and other 5-HT agents (22) on fat intake in studies in which rats have been offered a choice of protein, carbohydrate and fat rations. Consequently, there is some experimental evidence for effects of 5-HT agents upon both carbohydrate and fat intake.

There is good evidence that hyperphagia and obesity can be induced in rats by high fat and high carbohydrate cafeteria diets (7,20). More particularly, hyperphagia and body weight gain can be induced by chow diets supplemented by either fat (32) or carbohydrate in the form of sucrose or polysaccharides (34). In turn, it has previously been demonstrated that rats in the plateau phase of obesity induced by cafeteria diets are particularly sensitive to the anorectic and weight-reducing action of serotoninergic drugs such as d-fenfluramine (10,17). Accordingly, in the present experiment, rats were provided with chow diets supplemented with either fat or carbohydrate (sucrose) in order to induce hyperphagia and weight gain. After the initial period of

weight gain serotoninergic manipulation was carried out by administration of d-fenfluramine continuously for 40 days. The changes in energy intake and weight gain with the two supplemented diets were intended to directly compare the potency and selectivity of this drug to reduce the intake of fat or carbohydrate in a model believed to have some relevance for the maintenance of obesity in humans. In addition, the continued monitoring of energy intake and body weight with long-term drug administration made it possible to observe the rate of development of tolerance to d-fenfluramine.

METHOD

Subjects

Thirty-six female Lister hooded rats were housed individually and weighed between 203–297 g at the start of the study.

Diet

All animals had ad lib access to standard lab chow (Labsure, economy diet; 25% protein, 10% fat, 65% carbohydrate). Twenty-four animals received, in addition, ad lib access to one of two dietary supplements. They were beef drippings (pure fat) or icing sugar mixed with water to form a paste (pure carbohydrate). Both were presented in glass dishes and were of similar texture. The energy densities of the dietary components were as follows: chow 10.90 kJ/g; CHO supplement 15.23 kJ/g; fat supplement 36.63 kJ/g.

Design and Dosage

The use of two treatment conditions (drug and control) in addition to the three diet groups meant that the experiment conformed to a 2×3 design with each of the six groups containing six animals. Since the experiment was intended to reveal the long-term effect of pharmacological manipulation lasting for several weeks, the drug was administered in the drinking water in order to avoid the aversive consequences of twice daily IP injections or the disturbance caused by repeated application by gavage. Since administration via drinking water means that drug delivery is distributed (unevenly) over the day, only low doses have to be administered to ensure effective 24-hr drug levels. Therefore, d-fenfluramine was dissolved in the drinking water at the low concentration of 0.057 mg/ml tap water. This mild treatment is equivalent to a total daily dose of between 2.0–4.0 mg/kg and is quite sufficient to cause a marked suppression of food intake. Control groups received tap water only. Drug treatment lasted for a period of 40 days after which the drug was withdrawn and the experiment continued for a further 40 days. This prolonged period of measurement was designed to reveal whether energy intakes and body weight returned to predrug levels following the termination of drug administration.

Procedure

The first phase of the experiment involved animals being assigned to one of the three diet conditions and feeding freely for a period of 90 days. During this time the food was changed every 2 days and body weight measured every 4 days. Having established obesity in those animals provided with a dietary supplement, animals were allocated to drug or control conditions. On day 1 of treatment administration, each animals' body weight was recorded as was the weight of chow and supplement (if appropriate) and the bottle of drinking water. After 2 days each diet component was reweighed together with any spillage and fresh food was given. Two days later the water bottles were reweighed (noting whether any wastage of water had occurred) and the animals' body weight recorded. Consequently, the data recorded were food intakes for 2 days (measured every 4 days), 4-day water intakes measured every 4 days and the animal's body weights measured every 4 days. This cycle was repeated throughout the 40-day period of drug administration and for the remaining 40 days of the experiment following drug withdrawal.

TABLE 1

MEAN (SE) BODY WEIGHT (g) ON DAY 1 AND DAY 90 OF THE PRETREATMENT PHASE OF THE EXPERIMENT

	High CHO Diet	High Fat Diet	Chow Diet
Day 1	252.7 (8.3)	246.1 (4.6)	247.5 (6.3)
Day 90	304.7* (10.8)	302.5* (5.3)	265.7 (7.0)

*Significantly different from chow, $p<0.01$.

Data Analysis

Differences in energy intake, rate of weight gain and drug intake in the 3 diet conditions required careful data transformation and use of control data to permit comparison of the effect of the drug in each condition. Each drug-treated animal's change in body weight and total energy intake was subtracted from the appropriate control group mean and divided by the total amount of drug ingested, and means for all subjects in each diet condition computed. This procedure allowed the standardised body weight loss (g) or energy intake reduction (kJ) per unit drug administered (mg/kg) to be compared across the 3 diet conditions. Parametric statistical procedures such as 1- or 2-way analysis of variance were then employed (with Newman-Keuls post hoc test) to examine the effects of diet and drug treatment.

RESULTS

Pretreatment Access to Diets

Dietary supplementation with fat or carbohydrate during the 90 days prior exposure resulted in a greater than 50 g increase in mean body weight (Table 1). Animals receiving only chow increased their body weight by less than 20 g on average during this time [diet × time interaction, $F(2,30)=14.531$, $p<0.01$]. By day 90, the start of the experimental phase, both supplemented groups had significantly higher body weights compared to the chow group (Newman-Keuls, $p<0.01$). Data from 2 animals were not available for different parts of the study; their data have therefore been totally excluded from the analysis.

Water and Drug Intake

Table 2 shows the mean daily water intake of the six groups of animals during the drug treatment phase of the experiment. In the control groups, the chow-fed animals consumed most water and the fat-supplemented animals the

TABLE 2

MEAN (SE) DAILY WATER (ml) AND d-FENFLURAMINE (mg/kg) INTAKE DURING 40 DAYS DRUG TREATMENT

	High CHO Diet	High Fat Diet	Chow Diet
	Water Intake		
Control	24.0 (1.3)	20.7 (1.0)	30.6 (2.4)
Drug	18.4 (2.4)	16.8 (1.3)	21.8 (1.8)
	d-Fenfluramine Intake		
	3.81* (0.15)	3.28* (0.07)	4.97 (0.16)

*Significantly different from chow, $p<0.05$.

TABLE 3

MEAN (SE) DAILY ENERGY INTAKE (kJ) DURING 40 DAYS OF DRUG TREATMENT AND 40 DAYS WITHDRAWAL

	High CHO Diet	High Fat Diet	Chow Diet
	Drug Treatment (days 1–40)		
Control	254.9 (12.2)	288.2 (10.0)	223.2 (7.1)
Drug	207.8 (6.2)	232.2 (7.8)	207.9 (6.6)
% Reduction	−18.5	−19.4	−6.9
	Withdrawal (days 41–80)		
Control	259.9 (7.4)	287.0 (8.9)	229.0 (7.1)
Drug	297.7 (8.6)	288.0 (5.1)	238.9 (9.7)

TABLE 4

MEAN (SE) REDUCTION IN ENERGY INTAKE (kJ) AND AMOUNT OF BODY WEIGHT (g) LOST PER UNIT DRUG ADMINISTERED (mg/kg)

	High CHO Diet	High Fat Diet	Chow Diet
Energy Intake	14.42* (3.61)	18.34* (3.66)	4.21 (0.96)
Body Weight	0.29* (0.05)	0.25* (0.05)	0.09 (0.01)

*Significantly different from chow, $p<0.01$.

The figures in the body of the table represent the effectiveness of one mg/kg d-fenfluramine in lowering energy intake and body weight during the 40 day drug treatment phase for each of the diet conditions.

least, the differences in intake between these groups averaging 10 ml per day [main effect of diet, $F(2,28)=7.567$, $p<0.01$]. These group differences were maintained during treatment with d-fenfluramine though the drug decreased the overall intake by between 19 and 29% [main effect of drug, $F(1,28)=14.782$, $p<0.01$]. As the water intakes varied with the dietary regimes it follows that the amount of drug ingested in the three diet groups also differed. This effect of diet upon drug intake was significant, $F(2,14)=4.847$, $p<0.05$, with both supplemented groups receiving a significantly lower dose of d-fenfluramine than the group fed chow alone ($p<0.05$).

Energy Intake

Table 3 shows the effect of drug treatment and dietary regime on daily energy intake during the 2 phases of the experimental period. In the control groups, the animals which received the fat supplement had a significantly higher energy intake than those which received chow only [main effect of diet, $F(2,28)=5.393$, $p<0.05$; fat supplement significantly differed from chow group, $p<0.01$]. Energy intake was intermediate in the group with the CHO supplement. The upper portion of Table 3 shows that d-fenfluramine exerted a marked anorectic action in all 3 dietary groups [main effect of drug, $F(1,28)=12.328$, $p<0.01$]. The average reduction in energy intake varied between 7% (chow) and 19% (CHO and fat supplements). When these changes were corrected for the different drug intakes of the 3 groups, the standardised scores (decrease in energy intake per mg/kg of drug administered) indicate that the drug had a more potent anorectic action in the supplemented groups than in the chow-fed animals [$F(2,14)=5.157$, $p<0.05$; both supplemented groups significantly different from chow, $p<0.01$]. However, there was no difference in the potency of the drug with the carbohydrate or fat supplemented diet (Table 4). When the drug was withdrawn there was an immediate increase in energy intake with each dietary regime, although this increase was maintained only in the chow-fed and carbohydrate-supplemented animals.

The provision of two food sources in the supplemented groups provided the opportunity to examine the data for any specific effects of the drug upon the selection of carbohydrate or fat. Thus, Fig. 1 shows the intake of the supplementary diet (carbohydrate or fat) as a proportion of the total energy intake for the 2 supplemented dietary regimes. Considering the acute effect (first 2 days), the drug produced a small reduction in the proportion of fat consumed but had no effect on the carbohydrate supplement. Thereafter, d-fenfluramine-treated animals consumed the same proportion of fat as the nondrug controls, and at a higher level than the carbohydrate-supplemented animals [main effect of diet, $F(1,19)=9.491$, $p<0.01$]. However, with the carbohydrate-supplemented regime, drug-treated animals actually consumed a significantly greater proportion of calories as sucrose than did the nondrug controls, $t(9)=2.486$, $p<0.05$. This effect declined during the withdrawal period and had disappeared by days 72–80.

Body Weight

Figure 2 shows the change in body weight for each group over the 80-day experimental period. All drug-treated groups

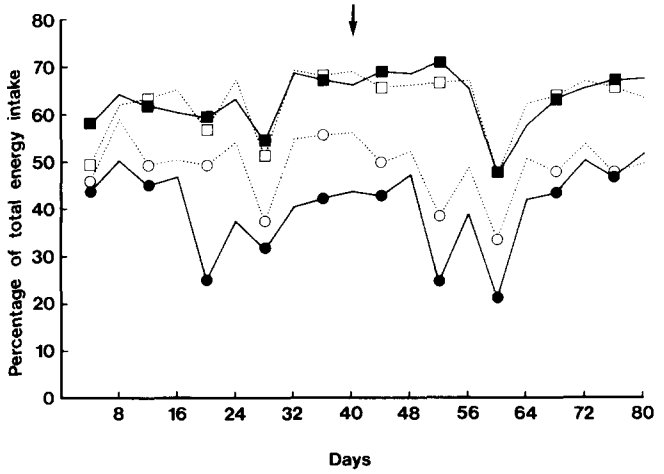

FIG. 1. The effect of d-fenfluramine (dotted lines, open symbols) on the intake of the CHO supplement (circles) and the fat supplement (squares), expressed as a proportion of the total energy intake. The arrow at 40 days indicates the time at which the drug was withdrawn.

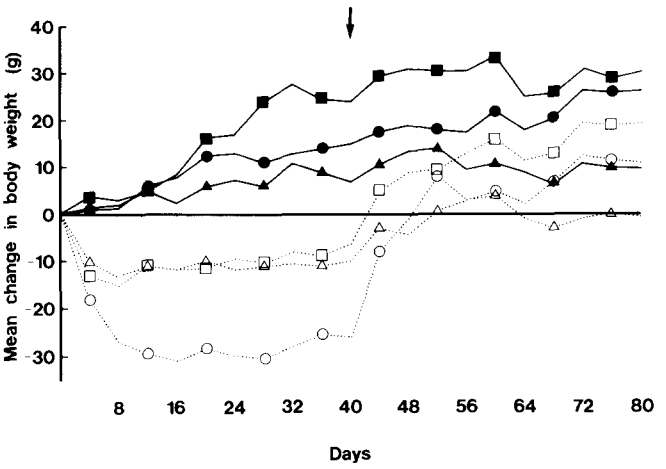

FIG. 2. The effect of d-fenfluramine (dotted lines, open symbols) on the mean change in body weight in CHO-supplemented (circles), fat-supplemented (squares) and chow-fed (triangles) animals. The arrow indicates time of drug withdrawal.

immediately lost weight. Animals that received the CHO supplement appeared to lose more than the other two groups. After the first 12 days of drug treatment body weight did not decline further and the animals maintained their weight at a constant level until the drug was withdrawn. Since untreated animals continued to gain weight during this period, the relative weight loss of the drug-treated groups also continued to increase. Upon withdrawal of the drug, body weight rapidly increased particularly during the first 12 days. The drug-treated animals, however, never fully recovered the weight lost relative to controls even by the end of the full 40-day withdrawal period.

The standardised changes in body weight (accomodating group differences in rate of weight gain and drug intake) described in Table 4 show a significant effect of diet upon the effectiveness of d-fenfluramine, $F(2,14)=7.401$, $p<0.01$. Both supplemented groups lost significantly more weight than the chow group ($p<0.01$) but the drug was *equally* effective in the fat and carbohydrate-supplemented groups.

DISCUSSION

This study has confirmed that a laboratory chow diet supplemented with a separate portion of a sweet carbohydrate (sucrose) or fat (beef lard) provokes moderate hyperphagia and body weight gain. Long-term administration of the serotoninergic drug d-fenfluramine exerted a more potent anorexic action in rats on the supplemented dietary regimes than in the chow-fed controls. This greater potency of d-fenfluramine in hyperphagic rats is consistent with a previous report on the effect of d-fenfluramine on rats eating a cafeteria-type diet which promoted hyperphagia (8). The effect appears similar to that reported earlier for the opioid blocking drugs naltrexone (2) and naloxone (27). d-Fenfluramine also brought about a more potent decrease in body weight in the diet-supplemented animals. This weight-reducing effect appeared to be proportional to the decrease in energy intake.

However, the data clearly showed that the superior potency of d-fenfluramine in the diet-supplemented animals was equivalent for the fat- and sucrose-treated groups. Over the 40-day period the drug brought about a 18.5% decrease in energy intake for the sucrose-supplemented group and a 19.4% decrease for animals provided with an additional fat ration. These deficits brought about respective weight losses of 0.29 and 0.25 g of body weight for every mg/kg of drug administered. The slimming effect of d-fenfluramine ceased as soon as the drug was withdrawn and the treated animals quickly gained weight. However, by the end of the experimental period (a further 40 days), the body weights of the previously drug-treated rats had stabilized below the body weights of the control animals.

It is worth mentioning that in this long-term study of pharmacological modulation of energy intake and body weight, even after 40 days of continuous drug administration, energy intakes were still well below those of control animals (over the last 10 days). In other words, tolerance to the drug-induced anorexia was not apparent with the supplemented groups. Intakes of chow-fed rats were equal for drug-treated and control groups after 40 days. A number of differences exist between the design of this study and the design of those experiments normally carried out to evaluate tolerance. First, rats were freely fed rather than being deprived or on a cyclic feeding regime. Second, energy intake was measured over 24 hours rather than being restricted to a brief period following drug injection. Third, a rather low daily dose of the drug was administered which was small in comparison with doses frequently used to investigate tolerance [e.g., (23)]. Fourth, the delivery system for the drug (drinking water) meant that the drug administration was distributed over the day rather than being concentrated into one or two daily doses. Fifth, diets were supplemented with hyperphagia-inducing nutrient supplements. These differences make comparisons with other experiments investigating tolerance rather difficult. However, the data clearly show that under certain experimental conditions the anorexic ca-

pacity of d-fenfluramine is maintained for at least 40 days. Moreover, the rate of development of tolerance to this drug-induced anorexia depends upon the nature of the diet.

The absence of tolerance noted in both the fat and sugar supplemented groups is consistent with the equivalent potency of the action of d-fenfluramine with these dietary regimes. However, it could be argued that measurement of total energy from the chow plus supplement in the supplemented regimes masked any selective effect of the drug on the supplement itself. This was not the case. When the drug's anorexic action on the supplement alone was plotted as a proportion of total energy intake, the percentage of fat consumed was equivalent for the drug-treated and control groups for the whole experimental period. The porportion of energy consumed as sucrose was significantly greater in drug-treated rats than in controls. This effect is reminiscent of a previous report of the acute action of fenfluramine (racemic compound) in rats offered chow plus a separate sucrose supplement (29). With fenfluramine, the sucrose intake was unchanged whilst chow intake was suppressed. A similar effect has also been demonstrated recently for the effect of d-fenfluramine on sucrose and polycose supplements presented in solution (21). These data are difficult to reconcile with those hypotheses suggesting a general carbohydrate suppressive effect of serotoninergic drugs (see Introduction).

The results clearly demonstrate that chronic administration of a drug known to release serotonin from presynaptic terminals [e.g., (16)] causes a general reduction in energy intake. This finding is in keeping with the suggested inhibitory role for serotonin in feeding control [e.g., (3, 5, 6, 19)]. However, for the present experiment, it must be considered whether the particular manner of administering the drug, via the drinking water, could have interfered with a proper understanding of the pharmacological action of d-fenfluramine. This is unlikely. First, although the drug treatment certainly reduced water intake, this suppression (about 20%) was similar to the suppression of energy intake (about 20%) and these values are within the normal range for the drug administered by the IP route. Second, since all dietary conditions received the drug in the same manner it is not easy to construct an argument for a suppression of water intake exerting a different influence on any particular dietary supplement. Consequently, this manner of introducing the drug into the animal's system does not appear to have exerted any major effect on the outcome. The changes observed therefore appear to have arisen because of the pharmacological action of the drug. It is worth noting that a recent study of chronic administration of d-fenfluramine using implanted minipumps also failed to detect a carbohydrate-suppressing effect (33). Indeed, the treatment inhibited protein intake.

Is this study a fair test of the action of a serotoninergic drug on carbohydrate intake? It could be argued that since the effect of dietary carbohydrate upon plasma amino acids and brain tryptophan only occurs when the diet contains less than about 4% protein, then any drug manipulation of serotonin upon preference will only occur with a diet of this type. However, this argument cannot be sustained. The theory embraces the idea that a drug like d-fenfluramine might "'fool the brain' into thinking that adequate carbohydrate had been ingested" (when in fact it had not) (37). Moreover, earlier experiments which provided the basis for the link between serotoninergic drugs and macronutrient intake were effective even though rats consumed significant amounts of protein (35,36). Therefore, the present experiment does constitute a fair test of the experimental hypothesis. The results add further information to enable researchers to make an evaluation about the robustness and strength of the underlying theory.

Taken as a whole, the results of this study indicate that the action of pharmacological agents upon food consumption is a complex phenomenon. The outcome of any study depends on the number of contextual variables (11) experimentally manipulated. In the study reported here the contextual variables of choice (chow vs. supplement), nutritional composition (carbohydrate vs. fat), taste (sweet vs. salty) and texture (pellets vs. paste) modified the effect of d-fenfluramine upon energy intake and body weight. The important theoretical issue of the action of serotoninergic drugs upon nutrient intake cannot be resolved by a single experiment. The manipulation of nutrients in experimental designs invariably means that a number of variables are simultaneously adjusted (4) and therefore a single experiment is not likely to be decisive. However, certain general findings can emerge. The present experiment, using a particular form of long-term drug administration, has confirmed that the anorexic potency of a serotoninergic drug like d-fenfluramine is enhanced under conditions which promote hyperphagia. This appears to be true for other agents such as opioid blockers (2,27), but not amphetamine (12). However, this antihyperphagic action does not depend upon the nutrient content of the diet and the present results do not provide evidence for a drug-induced specific carbohydrate suppressive action.

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