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d-Fenfluramine Selectively Suppresses Carbohydrate Snacking by Obese Subjects

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Twenty obese inpatients who claimed to crave carbohydrate-rich foods were given d-fenfluramine (15 mg p.o., twice daily) or its placebo, double-blind, for two consecutive eight-day periods. Food choices were measured on treatment days 1, 7, and 8 by giving the subjects access to unlimited portions of six isocaloric meal foods (three high in carbohydrate and three high in protein) and of 10 isocaloric snack foods (five high in protein and five high in carbohydrate) available 24 hours a day in a computerized vending machine. d-fenfluramine reduced mealtime calorie intake by only 16% (from 1940 ± 94 to 1630 ± 92; $p < .001$), mealtime carbohydrate by 22%, and had no significant effect on mealtime protein consumption; in contrast, snack calorie intake was reduced by 41% (from 707 ± 97 to 414 ± 46; $p < .001$), and snack carbohydrate intake by the same proportion. The mean number of carbohydrate-rich snacks consumed per day decreased from 5.8 ± 0.8 to 3.4 ± 0.4 ($p < .01$), while that of protein-rich snacks failed to change significantly (i.e., from 0.7 ± 0.2 to 0.5 ± 0.2).

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Although abundant evidence supports the view that overconsumption of calories can be a major factor in producing obesity, few direct measurements have been made of the foods that obese people actually choose, nor of their temporal patterns of food consumption. We previously described an experimental procedure that allowed us to characterize the snacking patterns of hospitalized obese subjects given ad libitum access to 10 common snack foods of varying nutrient contents (Wurtman, 1981). Using this procedure, we identified a subgroup of obese individuals who both claimed to have strong intermittent cravings for foods with high carbohydrate contents, and who actually snacked almost exclusively on such foods despite the equal accessibility of isocaloric protein-rich snack foods. Their consumption of snacks was not randomly distributed throughout the day, but rather was clustered within a 1- or 2-hr period specific for each individual. Treatment with *dl*-fenfluramine, an anorectic drug that selectively enhances serotonin-mediated neurotransmission (Garattini, 1975) significantly decreased their consumption of carbohydrate-rich snacks. However, since the subjects ate few or no protein snacks, and the nutrient composition of their meals was fixed, we were unable to determine whether these "carbohydrate-cravers" also chose disproportionately large amounts of carbohydrates at meals as well as snacks, nor whether mealtime nutrient composition or daily protein intake also was affected by fenfluramine treatment.

We now describe results of a study in which both meal and snack foods could be chosen, ad libitum, from a variety of common foods, and affirm that excessive carbohydrate intake among self-diagnosed obese "carbohydrate-cravers" is limited to their snacks, and not observed with their meals. Moreover, *d*-fenfluramine significantly diminishes carbohydrate snack intake but only slightly decreases the consumption of carbohydrate at mealtime. It has little effect on protein intake, at meals or as snacks.

METHODS

Subject Selection

Obese subjects were solicited through advertisements containing the key phrase, "overweight carbohydrate-cravers." To be accepted into the study, subjects had to be at least 15% heavier than ideal body weight (Metropolitan Height and Weight Table, 1983), in good health, and not pregnant nor taking medications. A questionnaire on food habits and an interview were used to determine whether the subject habitually overate carbohydrate-rich foods, especially as snacks. Prior to the study a physical examination was performed on each subject along with a urinalysis, a C.B.C. and blood chemistries including calcium, phosphorus, glucose, BUN, creatinine, cholesterol, total protein, triglycerides, bilirubin, alka-

line phosphatase, LDH, SGOT, and electrolytes (sodium, potassium, chloride, CO_2). Each subject signed a consent form approved by the Massachusetts Institute of Technology Committee on the Use of Humans as Experimental Subjects.

Subject Profile

Thirty subjects were accepted into the study, and data were used from 20 of them. Two subjects failed to complete the study because of family or work-related problems, and four because of health problems not related to the study. (One subject broke his leg, one subject reported lactose intolerance after being admitted to the study, hypertension was detected in one subject during the placebo treatment, and one subject had high blood glucose not detected during the prestudy medical screening.) The other four subjects did complete the study but their data were not used because of noncompliance with the protocol (one subject) or intercurrent gastrointestinal viral illnesses that caused them to stop eating during the study (three subjects). The 20 subjects whose data were used included 16 women and four men. Their ages ranged from 19 to 61 years (mean age: 41), and their percentage of body weight above ideal for their heights ranged from 17 to 85 (mean: 44).

Study Design

On four consecutive weeks, subjects were admitted to the MIT Clinical Research Center on Tuesday afternoons, and remained in the CRC until 8 a.m. on the following Friday morning. Baseline data on food intake were collected on the first and third Wednesdays of the study periods (days 0). Subjects received *d*-fenfluramine or its placebo according to a crossover design sequence; treatment order was randomized, and the experiment was performed double-blind. The first treatment period began on Thursday of the first study week and continued for eight days until 7 a.m. Friday of the second week, after which there was a five-day washout period; the second treatment period began on Thursday of the third study week and lasted until 7 a.m. Friday of the fourth week. Each treatment period thus lasted eight days, during which the effects of drug or placebo on food intake were measured on days 1, 7, and 8. No measurements of food intake were made during the outpatient period; however patients were instructed to refrain from consciously restricting food intake while at home. Fourteen subjects received, at random, the *d*-fenfluramine during the initial treatment period, while six initially received the placebo; no significant effect of treatment order was noted.

Drug Administration

Subjects received 30 mg of *d*-fenfluramine (Isomeride) or its placebo, packaged and coded by Servier Amerique (Paris, France), in two 15-mg doses daily, at 7 a.m. and 4 p.m.

Measurement of Food Intake

During the first, seventh, and eighth days of each treatment period as well as on the baseline days (days 0), subjects were instructed to consume all of their food from the meals and snacks provided in the Clinical Research Center. To minimize noncompliance, subjects were not allowed to leave the facility except for a 15-minute period once a day, under supervision.

Meals. Subjects could choose from among three high-carbohydrate (12–16 g of CHO) and three high-protein (12 to 16 g of protein) foods, provided in unlimted quantities, at each meal (Table 1). The six food items were isocaloric; high-fat ingredients such as butter or cream were added as ingredients to certain foods like pasta to increase their caloric values. The fat contents of the foods were kept constant so that we could measure specifically the effects of *d*-fenfluramine on the voluntary intake of carbohydrate and protein. Fat constituted an average of 55.5% of the calories in meals and 51.7% of the calories in the snacks. The foods were served in preweighed containers, which were reweighed after the meal was completed. The selection of foods presented at each meal remained constant throughout the study; the types of foods offered were selected to represent meal items normally consumed by individuals living in the Boston area. Skim milk (4 oz.) was offered at each meal, and a tossed salad was included with lunch and dinner.

Snacks. Subjects had, except during mealtimes, continuous access to 10 snacks; the snacks were stored in a refrigerated vending machine. Five of the snacks were high in protein (10–12 g), and five high in carbohydrate content (10–12 g) (Table 1); the snacks contained between 88 and 118 kcal, and were described as equally appetizing. The vending machine was linked to a digital interface containing microchips programmed to allow the subject to obtain any one of the 10 snacks after typing a personal access code on an attached keyboard. The microchips also recorded the identity of the subject, the type of snack removed, and the time that the snack was obtained. The vending machine was placed in a remote area of the CRC so that the subjects could obtain snacks unobserved by the staff and other patients.

Subjects were told to consume each snack as soon as it was obtained and not to save one snack in order to eat it with another; this was to preclude the mixing of protein and carbohydrate snacks. The subjects were

Table 1. Nutrient contents of foods offered at meals and snacks.

	kcal	Protein (g)	CHO (g)	Fat (g)
Breakfast				
English muffin with butter	134	2.8	14.1	7.3
Waffle with butter and diet syrup	134	2.3	16.5	6.7
Quaker Natural Cereal	127	3.6	17.0	6.2
Canadian bacon	150	15.0	0.3	9.6
Cottage cheese with sour cream	130	15.0	3.4	6.0
Cheese omelet	140	14.0	3.0	7.0
Lunch				
Bagel (1/2) and cream cheese	190	5.2	16.0	12.0
Bran muffin with butter	184	2.4	17.0	13.0
Potato salad	217	2.4	17.0	16.0
Kielbasa, cheese, turkey plate	195	15.0	1.3	14.0
Turkey salad	211	17.0	0.4	15.0
Crustless quiche	212	15.0	5.0	15.0
Dinner				
Scalloped potato	190	3.0	19.0	12.0
Spanish rice with butter	185	1.5	15.0	12.0
Macaroni with garlic butter	209	3.0	18.0	14.0
Chicken fricassee	220	16.0	2.5	18.0
Beef Stroganoff	202	16.0	3.0	15.0
Baked haddock with tartar sauce	200	15.0	2.0	15.0
Snacks				
Hershey bar	108	1.4	11.0	6.0
Doughnut holes	111	1.0	12.0	7.0
Cheese tidbits	108	1.4	11.0	6.4
Ritz crackers	90	1.2	11.0	5.0
Pecan Sandies	108	1.0	12.0	6.0
Barbecued chicken wings	108	12.0	1.0	6.0
Mozzarella cheese and honey loaf (luncheon meat)	111	12.0	2.0	6.0
Bacon Twirls	88	11.0	0	4.6
Boiled ham and cheese	118	13.0	0.6	7.0
Corned beef	111	12.0	1.4	7.1

also told that an individual, long-term reducing diet would be developed for them based on their intake of calories and nutrients during the placebo treatment period, and thus it was critical that we obtain an accurate record of what they actually consumed at a time that they were maintaining their weight. They were told to inform the staff if they took a snack and did not consume it; their rooms were checked by the ward housekeeper for hoarding.

Data Analyses. Data on food consumption were manually stored in an RS 1 data base management system (Bolt, Beranek and Newman, Inc., Cambridge, MA), which also was used for data analyses. A three-way analysis of variance followed by paired *t*-tests was used to assess the effects of *d*-fenfluramine on calorie and nutrient intake. The analyses in-

cluded the effect of *d*-fenfluramine on total calorie and nutrient intake, meal calorie and nutrient intake, and snack calorie and nutrient intake. Fat intake could not be varied independently of protein and carbohydrate consumption, since fat was a constant proportion of all foods offered.

RESULTS

Calorie and Nutrient Intake During the Placebo Period

During the placebo period, subjects consumed 73% (1940 ± 97 kcal) of their total daily calories (2650 ± 80 kcal) from meals, and mealtime carbohydrate and protein intakes were about equal (Table 2). They ate many more carbohydrate-rich than protein-rich snacks (5.8 ± 0.8 vs 0.7 ± 0.2; $p < .001$; Table 2), consuming about 35% of their total daily carbohydrate intake from snacks (67 ± 9.0 g of CHO in snacks vs 121 ± 8.4 g at meals). Six of the 20 subjects consumed no protein snacks at all.

The consumption of carbohydrate snacks was concentrated within the afternoon and evening time periods. Peak periods of snack intake occurred between 2 to 3 p.m. and 7 to 10 p.m. (Fig. 1); about twice as many total snacks were consumed in the evening as in the afternoon (230 vs 141; Fig. 1).

Effect of *d*-Fenfluramine on Calorie and Nutrient Intake

d-Fenfluramine significantly reduced mean calorie intake both as snacks (414 ± 46 vs 707 ± 97 kcal; $p < .001$) and at meals (1630 ± 92 vs 1940 ± 94 kcal; $p < .001$) in the group as a whole (Fig. 1; Table 2); however, the reduction in snack calories was more pronounced (41% vs 16%). The reduction in carbohydrate-rich snacks consumed during *d*-fenfluramine treatment (5.8 ± 0.8 vs 3.4 ± 0.4; $p < .01$; Table 2) accounted for the decrease in snack calorie intake; consumption of protein-rich snacks during both the placebo (0.7 ± 0.2) and *d*-fenfluramine (0.5 ± 0.2) periods was too infrequent to be affected significantly by the drug. *d*-Fenfluramine administration also reduced mealtime carbohydrate consumption ($p < .01$) (Table 2), but by a lesser proportion (22%) than it decreased snack carbohydrate intake (41%). *d*-Fenfluramine failed to affect mealtime protein or fat intake significantly.

Although *d*-fenfluramine significantly decreased the calorie consumption from snacks and meals of the group as a whole, snack calorie consumption actually *increased* by 34% ($p < .005$) in six of the 20 subjects. Retrospective analysis of the data to identify characteristics that might have predicted nonresponse to *d*-fenfluramine indicated that, while mealtime food intake during the placebo period for these six subjects was similar to that of the other 14, the nonresponders consumed significantly

Table 2. Effect of *d*-fenfluramine on meal and snack nutrient composition.

				Meal (g/day)				Snacks (number/day)			
				Carbohydrate		Protein		Carbohydrate		Protein	
Subject	Sex	Age	I.B.W. (%)	P	F	P	F	P	F	P	F
1	F	35	145	131	94	113	81	8.0	2.3	1.0	0.7
2	F	45	130	94	85	74	70	5.7	1.0	0.3	0.3
3	F	46	173	61	58	105	99	9.0	4.0	1.7	1.0
4	F	35	117	96	70	72	62	3.0	1.7	0.3	0.0
5	F	47	185	126	99	122	112	4.6	3.3	1.0	4.0
6	F	39	134	78	63	74	80	2.3	4.7	1.3	0.3
7	M	39	140	217	167	156	131	3.6	4.3	0.3	0.7
8	F	53	117	136	78	111	80	2.0	1.0	0.3	0.7
9	F	38	147	126	78	134	117	6.7	4.0	0.7	0.0
10	F	24	157	180	146	119	108	6.3	3.3	1.0	0.0
11	F	52	145	156	106	96	92	6.0	3.3	0.0	0.0
12	F	28	141	101	122	81	98	8.7	6.7	3.3	1.3
13	F	28	184	129	133	89	107	5.6	6.7	0.0	0.0
14	M	40	139	119	97	165	144	4.7	3.7	0.3	0.0
15	F	58	163	85	68	101	92	1.0	4.0	0.0	0.0
16	F	19	149	100	71	107	68	16.3	3.7	3.0	0.0
17	F	31	129	94	46	87	52	4.0	1.3	0.0	0.0
18	F	37	136	98	66	63	58	8.7	3.7	0.0	0.0
19	M	60	134	192	127	72	75	7.7	0.7	0.0	0.0
20	M	61	122	95	92	140	115	1.3	4.7	0.3	0.0
Mean ± SEM				121 ±8.4	94 ±6.7	104 ±6.1	93 ±5.2	5.8 ±0.75	3.4 ±0.36	0.7 ±0.20	0.5 ±0.20

Percentage of ideal body weight was determined in terms of each subject's height and body habitus, using the 1983 Metropolitan Life Insurance Company Tables. P = placebo; F = fenfluramine.

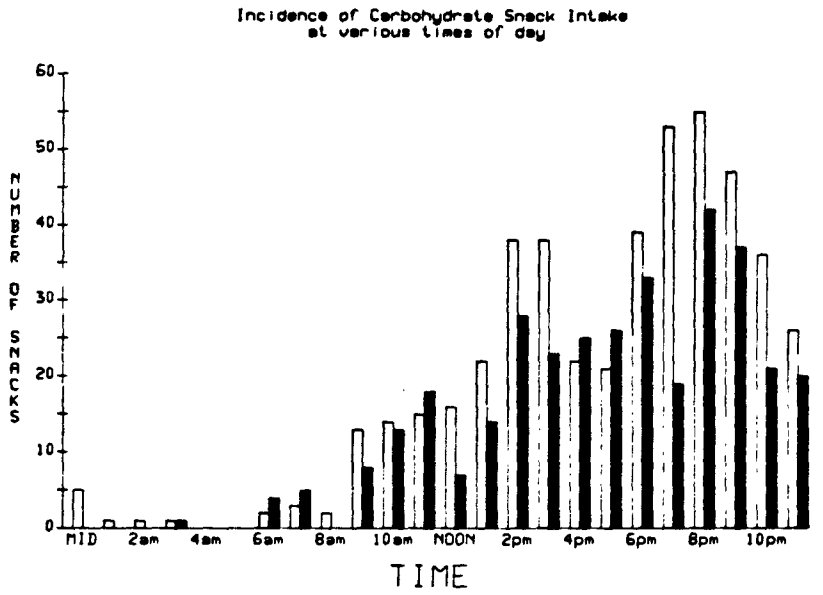

Figure 1. Data represent the total number of carbohydrate-rich snacks taken during each hour of the day and night by the 20 subjects during three placebo days (open bars) and three days of *d*-fenfluramine treatment (15 mg/p.o. twice daily; closed bars). Each bar represents snacks consumed during the hour ending at the time indicated. Subjects had breakfast at 8:00 to 8:30 a.m.; lunch at 12:15 to 12:45 p.m. and dinner at 5:00 to 5:30 p.m.; they were not allowed to take snacks during these meal intervals. Each subject consumed an average of 5.7 carbohydrate-rich snacks and 0.7 protein-rich snacks per day during the placebo period.

fewer carbohydrate snacks per day while on the placebo (3 ± 0.8 vs 7 ± 1; $p < .001$). (Consumption of protein-rich snacks did not differ between the two groups.) There was no relationship between age, sex, percentage of ideal body weight, or treatment order and whether or not an individual responded to *d*-fenfluramine by decreasing his or her snack intake.

DISCUSSION

These data show that obese subjects self-described as carbohydrate-cravers consume many more carbohydrate-rich than protein-rich foods as snacks, but choose to eat similar amounts of these nutrients at meals (Table 2); thus they corroborate their self-description as carbohydrate-cravers. Their consumption of carbohydrate snacks is not randomly distributed throughout the day and evening but, instead, is clustered within the midafternoon and midevening periods (Fig. 1). Their preference for

carbohydrate-rich over protein-rich snack foods is not due to any restriction in the availability of carbohydrates at mealtime, since subjects had unlimited access to high-carbohydrate and high-protein foods at both meals and as snacks. Moreover, their overconsumption of carbohydrate-rich snacks cannot simply reflect the desire to end their meals with sweet, dessert-like foods since, in our study, most of the snacks were consumed several hours after the meals had ended.

The mealtime calorie and nutrient intakes of our subjects were well within the ranges suggested by the Food and Nutrition Board of the United States National Academy of Sciences (RDA). The subjects' calorie intake from meals was probably insufficient to account for their obesity, and the moderate amount of carbohydrate consumed at meals alone would not characterize the subjects as individuals with a particularly unusual appetite for carbohydrate-rich foods. However the sizable proportion of total daily calorie intake that they consumed as snacks, and their overwhelming propensity to choose carbohydrate-rich snacks, suggest that this snacking behavior was a major factor in their obesity (and that their claims of periodically craving carbohydrate-rich foods were indeed accurate). These observations demonstrate the importance of measuring total daily meal and snack-food intakes in analyzing the eating behavior of overweight individuals, and of allowing subjects in such studies to choose among real foods of differing nutrient contents.

Our observations also demonstrate that while *d*-fenfluramine reduces food intake from both snacks and meals, it exerts its greatest effect on snack carbohydrates, and a smaller but significant effect on meal carbohydrates, without significantly diminishing protein intake, either at meals or as snacks. [Among the seven subjects who ate one or more protein-rich snack per day, *d*-fenfluramine did reduce protein snack intake from 1.7 to 1.0 snacks per day ($p < .05$). However, it failed to diminish their mealtime protein intakes, or their total daily protein intakes.] Fat intake, at meals or snacks, was not significantly decreased after drug treatment. Evidence that *d*-fenfluramine can selectively suppress carbohydrate intake has also been obtained from studies on experimental animals (Wurtman, 1979a,b; Moses & Wurtman, 1984). Amphetamine, unlike *d*-fenfluramine, reportedly causes a nonspecific reduction in food intake by humans, decreasing protein and carbohydrate consumption to an equal extent (Blundell, 1979).

The fact that *d*-fenfluramine was most effective in decreasing carbohydrate intake when subjects were able to consume the carbohydrate without concurrently eating much protein (i.e., as carbohydrate-rich snacks) may be related to its actions on brain serotonin. Consumption of a carbohydrate-rich, protein-poor meal accelerates the synthesis and release of brain serotonin (Fernstrom, 1972); this is followed by a decrease in the proportion of carbohydrate chosen for consumption in the next meal (Wurtman, 1983). Protein-rich meals have opposite effects on brain

serotonin (Fernstrom, 1972). Drugs like *d*-fenfluramine, which enhance serotonin-mediated neurotransmission, can also suppress carbohydrate intake selectively (Wurtman, 1979a,b; Moses & Wurtman, 1984). When tested in animals, these drugs suppress food consumption only when the ratio of carbohydrate to protein in the test diet is high, i.e., only when the test diet would be expected to enhance brain serotonin synthesis (Wurtman, 1979a,b; Moses & Wurtman, 1984). The carbohydrate–protein ratio (g/g) in the snacks that our subjects consumed during the placebo period was 67:9, or 7.4 to 1; the ratio at meals was only 121 to 104, or 1.2 to 1. Thus the relatively greater effect of *d*-fenfluramine on snack than on meal consumption may have been related to the fact that the carbohydrate-to-protein ratio of the snack foods chosen for consumption was very high, while the ratio in the foods chosen at meals was low.

Observations on the relationship between carbohydrate consumption and mood suggest that carbohydrate-rich foods may be chosen by some individuals because of their ability to facilitate a desired emotional state. In a study of 184 normal adult men and women who consumed either a protein-rich or carbohydrate-rich breakfast or lunch, Spring, Maller, Wurtman, and Digman (1983) found that lunchtime carbohydrate consumption caused male subjects to feel more relaxed and calm, and female subjects to feel drowsy; conceivably, these mood changes may be desired by some subjects at the times of day that they elect to eat carbohydrate-rich foods. A relationship between depression and carbohydrate hunger in a subgroup of psychiatric patients has been described by Rosenthal, Sack, and Gillin (1984); symptoms became manifest each year during the seasons of decreasing daylength, i.e., fall and winter. Carbohydrate hunger among this subgroup increased during the fall and winter, when depression was worst, and lessened, along with the depression, in the spring and summer. Using a standardized questionnaire (SADS-L Test; Endicott, 1978) we examined the possibility that carbohydrate-craving might also be associated with a tendency towards affective disorders, using seven of our subjects chosen at random after completion of the present study (one male and six female). All seven acknowledged having experienced at least two episodes of major depression; two had undergone suicidal episodes. Three had experienced periods of hypomania, two frequently. (None of these depressive or hypomanic episodes occurred during the period in which the subjects participated in our study.) These findings invite speculation that obesity resulting from carbohydrate-craving may, in some subjects, reflect an unrecognized desire to eat foods that will produce desired changes in affective state.

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