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Differential Effects of Amphetamine and Fenfluramine on Dietary Self-Selection in Rats[1]

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ORTHEN-GAMBILL, N. AND R. B. KANAREK. *Differential effects of amphetamine and fenfluramine on dietary self-selection in rats.* PHARMAC. BIOCHEM. BEHAV. **16**(2) 303–309, 1982.—Daily caloric intakes and dietary self-selection of the three macronutrients, protein, fat and carbohydrate were examined in female rats following administration of d-amphetamine sulfate (0.0, 0.5, 1.0 and 2.0 mg/kg, IP) or fenfluramine hydrochloride (0.0, 1.5, 3.0 and 6.0 mg/kg, IP). Animals were maintained on ground Purina Chow or one of two self-selection regimes, one with a high-caloric fat ration (7.85 kcal/g) and the other with a fat ration isocaloric to the carbohydrate and protein rations (3.76 kcal/g). Animals received drug injections at the beginning of a daily 8-hour feeding period with nutrient intakes measured at 2, 4 and 8 hrs following injections. While both amphetamine and fenfluramine led to dose-related decreases in total caloric intakes, the two drugs resulted in different temporal patterns of feeding. Amphetamine produced its greatest effect on caloric intake during the first 2 hours of the feeding period, whereas fenfluramine suppressed caloric intake equivalently across the 8-hour feeding period. The two anorectic drugs also led to different patterns of nutrient choice. When animals were given the high-caloric fat ration, amphetamine selectively decreased fat intake while fenfluramine produced decreases in both protein and fat intakes, sparing carbohydrate intake. In contrast, when animals were given the isocaloric fat ration, amphetamine resulted in a general suppression of nutrient intakes while fenfluramine led to a sustained decrease in fat intake with a relative sparing of protein and carbohydrate consumption.

Dietary self-selection Protein Fat Carbohydrate Amphetamine Fenfluramine Anorexia Food intake

WHILE the administration of both amphetamine and fenfluramine lead to decreases in food intake, these drugs are hypothesized to produce their anorectic effects through different neurochemical pathways (e.g., [3, 4, 5, 6, 12, 14]). Most probably, amphetamine derives its anorectic potency from drug-induced alterations in brain catecholamine-containing neural systems, while fenfluramine's anorectic actions are mediated primarily by serotonin-containing systems. Both drugs release and block reuptake of their respective neurotransmitters with the resulting increase in synaptic availability of the neurotransmitter thought to be the primary cause of the acute anorectic effects of the drugs (e.g., [3, 4, 5, 6, 12, 14]).

In addition to acting through different neurochemical systems, recent evidence indicates that these two anorectic agents differentially affect temporal patterns of food intake [7, 8, 13]. Doses of amphetamine and fenfluramine which led to similar decreases in food intake measured over a two-hour period, produced distinctive anorectic profiles when food intake was monitored continuously. Amphetamine delayed the initiation of feeding, whereas fenfluramine allowed feeding to begin normally, but produced an early termination of feeding behavior [7,8]. Further, amphetamine led to frequent short bursts of rapid eating, while fenfluramine resulted in an overall decrease in the rate of food intake [7,8].

Typically, studies investigating the effects of anorectic drugs on food intake in experimental animals use only a single nutritionally complete diet. While conclusions on the effects of drugs on total energy intake can be drawn from these studies, no information on specific macronutrient intakes can be gathered. Amphetamine and fenfluramine, however, may have very different effects on intakes of the three macronutrients, protein, fat and carbohydrate [9, 15, 24, 25]. For example, following the administration of fenfluramine, weanling rats given simultaneous access to two isocaloric diets, one containing 5% protein and the other 45% protein, preferentially decreased their intake of the low-protein diet [24]. This pattern of intake resulted in a reduction in total energy intake with no significant decrease in protein intake. In contrast to fenfluramine, amphetamine administration led to proportional decreases in the intakes of both diets [24]. Unfortunately, it is difficult to draw clear conclusions from these data as the two diets used in the study varied not only in the percentage of protein they con-

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tained, but also, in the percentage of carbohydrate. The low-protein diet contained 80% carbohydrate, while the high-protein diet contained only 45% carbohydrate. The proportion of the third macronutrient, fat, was identical (15%) in both diets, so no conclusions can be drawn about drug effects on the intake of this macronutrient. Recent work indicates, however, that fat intake may be selectively affected by anorectic drugs [15]. When animals were offered separate sources of the three macronutrients, amphetamine injections led to a sustained suppression in fat intake across a six-hour feeding period. In contrast, protein and carbohydrate intakes were suppressed for only the initial two hours of the six-hour feeding period. As the fat component contained more calories per gram than either the protein or carbohydrate component, it is possible that the prolonged suppression of fat intake observed following amphetamine administration was due to the greater caloric density of the fat component. The use of isocaloric macronutrient rations would clarify whether amphetamine differentially affects fat intake. In the present experiment, two self-selection regimes were used, one with a fat ration that was more calorically dense (7.85 kcal/g) than the protein and carbohydrate rations (3.76 kcal/g), and the other with isocaloric sources of the three macronutrients.

In the second experiment, the effects of fenfluramine on nutrient selection were investigated using the same two self-selection regimes that were used in the first experiment. As in both experiments, animals were provided with separate sources of the three macronutrients, possible selective drug effects on specific macronutrient intakes could be evaluated.

TABLE 1

COMPOSITION OF DIETARY RATIONS FOR ANIMALS MAINTAINED ON THE SELF-SELECTION REGIMES

Protein Ration (3.76 kcal/g)
960 g Casein (ICN Pharmaceuticals)
40 g U.S.P. Salt Mixture (ICN Pharmaceuticals)
20 g Vitamin Diet Fortification Mixture (ICN Pharmaceuticals)
Carbohydrate Ration (3.76 kcal/g)
580 g Corn Starch (Teklad Test Diets)
280 g Dextrin (Teklad Test Diets)
100 g Commercial-grade Sucrose
40 g U.S.P. Salt Mixture
20 g Vitamin Diet Fortification Mixture
High-caloric Fat Ration (7.85 kcal/g)
912 g Commercial-grade Vegetable Fat (Crisco)
48 g Safflower Oil (Hollywood Health Foods)
90 g U.S.P. Salt Mixture
50 g Vitamin Diet Fortification Mixture
Isocaloric Fat Ration (3.76 kcal/g)
403 g Crisco
536 g Alphacel (ICN Pharmaceuticals)
21 g Safflower oil
40 g U.S.P. Salt Mixture
22 g Vitamin Diet Fortification Mixture

Vitamins and minerals were added to the components so that the three dietary rations contained equal amounts of the micronutrients on a per kilocalorie basis.

EXPERIMENT 1

METHOD

Animals

Eighteen female Sprague-Dawley rats (CD outbred, Charles River Laboratories, Wilmington, MA), with a mean body weight of 175 g at the beginning of the experiment, were used. Animals were housed individually in standard stainless steel laboratory cages in a temperature-controlled room (21±1°C), with a 12–12 hour light-dark cycle (lights on: 0800–2000 hours).

Procedure

Animals were randomly assigned to one of three dietary conditions: (1) a standard laboratory diet (N=6), consisting of ground Purina Laboratory Rodent Chow 5001 (caloric density=3.60 kcal/g), (2) a self-selection regime (N=6), consisting of three dietary rations: fat (caloric density=7.85 kcal/g), protein (caloric density=3.76 kcal/g) and carbohydrate (caloric density=3.76 kcal/g), and (3) a self-selection regime (N=6) with the same protein and carbohydrate components as above, but with a fat ration (caloric density=3.76 kcal/g) isocaloric to the protein and carbohydrate components (see Table 1 for diet composition). All dietary components were presented in Wahmann (Timonium, MD) LC-306A non-spill food cups, with the exception of the high-fat ration which was provided in 75 ml glass cups.

To allow for adjustment to dietary conditions, all animals were given ad lib access to their respective diets for 15 days. After this initial adjustment period, access to the respective diets was limited to eight hours per day (0900 to 1700 hour). Animals were given 18 days to adjust to the eight-hour feeding schedule. Ad lib access to water was provided throughout the experiment. During the entire pre-drug period, food intakes, water intakes and body weights were measured daily.

On the day preceding each drug injection day, animals received intraperitoneal (IP) injections of physiological saline at 0900 hour. On test days, animals in each dietary condition received IP injections of d-amphetamine sulfate (Smith, Kline and French, Philadelphia, PA). Amphetamine was dissolved in 0.9% saline to concentrations that allowed studied doses to be injected in volumes of 0.2 ml per 100 g body weight. Three doses of amphetamine were used: 0.5, 1.0 and 2.0 mg/kg body weight. Each animal received each dose of the drug twice, in random order. Nutrient intakes were measured at two, four and eight hours following the administration of either saline or amphetamine. Drug injections were separated by a minimum of six days.

Data were analyzed by one-way analyses of variance with repeated measures, followed by a posteriori comparisons between the different treatment levels using Scheffe's procedure [23]. Means for the two administrations of each dose of the drug, and means for saline injections were used in data analyses. All results reported as significant have a p value of less than 0.05.

RESULTS

Animals Maintained on Ground Purina Laboratory Chow

Amphetamine administration led to dose-related decreases in Purina Chow intake during the first two hours of

TABLE 2

TOTAL CUMULATIVE CALORIC INTAKES OF ANIMALS MAINTAINED ON PURINA CHOW OR A DIETARY SELF-SELECTION REGIME AT 2, 4 AND 8 HOURS AFTER THE ADMINISTRATION OF AMPHETAMINE

			2 Hours	4 Hours	8 Hours
	Saline		34.0	52.5	63.2
Purina	0.5 mg/kg		21.0	45.1	65.5
Chow	1.0 mg/kg	Amphetamine	12.1†	36.4	51.5
	2.0 mg/kg		2.0†	24.0†	56.5
	Saline		39.1	56.0	67.2
High-fat	0.5 mg/kg		13.9†	42.0†	52.1
Self-selection	1.0 mg/kg	Amphetamine	11.1†	35.0†	48.0*
Regime	2.0 mg/kg		7.3†	20.0†	40.1†
	Saline		31.3	51.5	62.0
Isocaloric	0.5 mg/kg		15.1†	34.0*	57.1
Self-selection	1.0 mg/kg	Amphetamine	7.0†	24.1†	55.0
Regime	2.0 mg/kg		4.0†	13.4†	41.4

Significantly different from saline: *=$p<0.05$; †=$p<0.01$.

the eight-hour feeding period (Table 2). By four hours after injection, only the high dose of the drug continued to significantly suppress caloric intake. At eight hours post-injection, Purina Chow intake did not vary as a function of drug administration.

Animals Maintained on the Dietary Self-Selection Regimes

Total caloric intakes. Following saline injections, total caloric intakes (calculated as the sum of caloric intakes from the three macronutrient components) of animals on the two self-selection regimes were similar to caloric intakes of animals given Purina Chow (Table 2).

Like animals given Purina Chow, animals on the self-selection regimes displayed dose-related reductions in total caloric intakes following amphetamine administration (Table 2). Animals given the self-selection regime with the high-caloric fat ration displayed significant decreases in caloric intakes at both two and four hours post-injection following all three doses of the drug. At eight hours post-injection, only the medium and high doses of the drug continued to suppress caloric intake.

Total caloric intakes for animals given the self-selection regime with the isocaloric fat ration were significantly decreased by all three doses of the drug at both two and four hours post-injection.

Individual macronutrient intakes. For animals maintained on the standard self-selection regime, amphetamine led to dose-related decreases in the intakes of all three macronutrients at two hours post-injection (Fig. 1). Intake of the fat component continued to be suppressed in a dose-related manner at both four and eight hours post-injection. In contrast, by four hours post-injection only the high dose of amphetamine significantly suppressed carbohydrate and protein intakes. Neither protein nor carbohydrate intakes varied as a function of drug administration by eight hours post-injection.

In contrast to the selective and prolonged suppression of fat intake seen in animals maintained on the self-selection regime with the high-caloric fat ration, animals given isocaloric sources of the three macronutrients displayed more general reductions in macronutrient intakes after amphetamine injections (Fig. 2). At two hours post-injection all three doses of amphetamine led to significant dose-related decreases in intakes of all three macronutrients. By four hours post-injection only the high dose of the drug significantly suppressed protein intake, both the medium and high doses significantly suppressed fat intake, and all three doses significantly suppressed carbohydrate intake. In contrast to the selective suppression of fat intake seen at eight hours following amphetamine administration in the group given the high caloric fat ration, a suppression of all three macronutrients was seen in the group given the isocaloric rations.

EXPERIMENT 2

METHOD

Animals

Eighteen naive female Sprague-Dawley rats (CD outbred) with a mean body weight of 175 g at the beginning of the experiment, were used. Animals were maintained under the same conditions as those in Experiment 1.

Procedure

The procedure was identical to that of Experiment 1 with the exception that the doses of fenfluramine hydrochloride (A. H. Robins, Richmond, VA) used were 1.5, 3.0 and 6.0 mg/kg body weight. Each animal received each dose of the drug twice, in random order. Drug injections were separated by a minimum of six days.

RESULTS

Animals Maintained on Ground Purina Chow

Fenfluramine injections led to dose-related decreases in Purina Chow intake throughout the entire eight-hour feeding

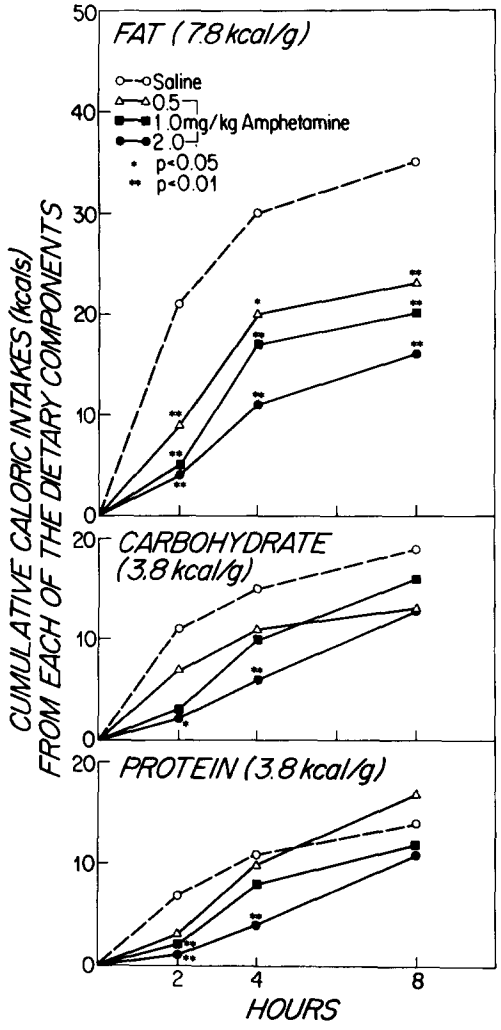

FIG. 1. Mean cumulative caloric intakes from fat, carbohydrate and protein across an eight-hour feeding period of animals maintained on a self-selection regime with a high-caloric fat ration following injections of saline, 0.5, 1.0 and 2.0 mg/kg amphetamine. Significantly different from saline: *=$p<0.05$; **=$p<0.01$.

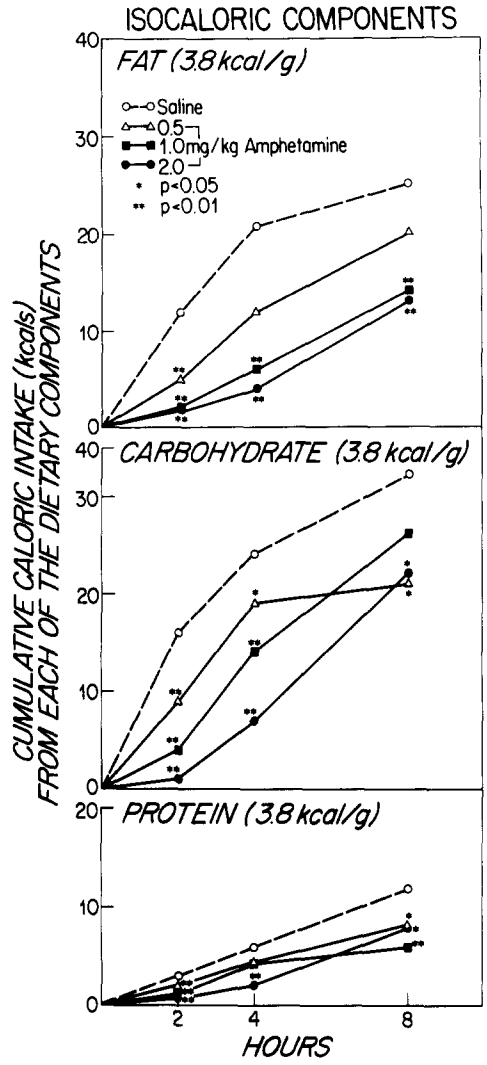

FIG. 2. Mean cumulative caloric intakes from fat, carbohydrate and protein across an eight-hour feeding period of animals maintained on a self-selection regime with isocaloric macronutrient components following injections of saline, 0.5, 1.0 and 2.0 mg/kg amphetamine. Significantly different from saline: *=$p<0.05$; **=$p<0.01$.

period (Table 3). While the decrease in caloric intake was not significant following the low dose of fenfluramine at any point in the eight-hour period, both the medium and high doses of the drug resulted in significant decreases in caloric intakes at all measurement times.

Animals Maintained on the Dietary Self-Selection Regimes

Total caloric intakes. Total caloric intakes of animals on the two self-selection regimes were similar following saline injections to intakes of animals maintained on Purina Chow (Table 3).

Animals on both self-selection regimes displayed dose-related decreases in total caloric intakes following fenfluramine administration. For the group given the high-caloric fat ration, all three doses of the drug resulted in significant decreases in total caloric intakes throughout the entire eight-hour feeding period. For the group given the isocaloric fat ration, the medium and high doses of the drug also significantly reduced total caloric intakes at all measurement points in the eight-hour period. The low dose of the drug resulted in a significant decrease in caloric intake only at two hours post-injection.

Individual macronutrient intakes. For animals maintained on the self-selection regime with the high- caloric fat ration, both fat and protein intakes were significantly decreased by all three doses of fenfluramine across the entire eight-hour feeding period (Fig. 3). In contrast, carbohydrate intake was not decreased by either the low or medium dose of the drug. Only the high dose of fenfluramine led to significant reductions in carbohydrate intake at two and four hours post-injection.

TABLE 3

TOTAL CUMULATIVE CALORIC INTAKES OF ANIMALS MAINTAINED ON PURINA CHOW OR A DIETARY SELF-SELECTION REGIME AT 2, 4 AND 8 HOURS AFTER THE ADMINISTRATION OF FENFLURAMINE

			2 Hours	4 Hours	8 Hours
	Saline		39.0	59.1	72.2
Purina	1.5 mg/kg		38.3	48.0	63.3
Chow	3.0 mg/kg	Fenfluramine	25.0*	35.1†	49.0†
	6.0 mg/kg		10.0†	15.1†	34.1†
	Saline		32.5	53.0	62.2
High-fat	1.5 mg/kg		23.2*	31.0†	41.1†
Self-selection	3.0 mg/kg	Fenfluramine	22.0†	27.1†	32.0†
Regime	6.0 mg/kg		14.0†	22.2†	25.0†
	Saline		37.3	51.5	65.0
Isocaloric	1.5 mg/kg		27.0*	46.0*	58.0
Self-selection	3.0 mg/kg	Fenfluramine	15.9†	24.0†	38.1†
Regime	6.0 mg/kg		11.0†	15.1†	28.1†

Significantly different from saline: *=$p<0.05$; †=$p<0.01$.

For animals receiving the isocaloric macronutrient components, fat intake was significantly suppressed by both the medium and high doses of fenfluramine at all measurement times. The low dose of the drug also resulted in a significant reduction in fat intake at two and four hours post-injection, however, by eight hours after injections, the reduction was no longer significant. Carbohydrate intake was significantly reduced at all measurement times during the eight hour feeding period by only the high dose of fenfluramine. The medium dose of the drug led to a significant decrease in carbohydrate intake measured at four hours post-injection. Protein intake was not suppressed by any of the doses of fenfluramine at any point during the eight-hour feeding period.

GENERAL DISCUSSION

In the present experiments, administration of both amphetamine and fenfluramine resulted in dose-related decreases in energy intake. However, as previously reported [7, 8, 13], the two drugs led to rather different patterns of food intake. Both for animals maintained on Purina Chow and for those maintained on the self-selection regimes, amphetamine administration produced its greatest effect on caloric intakes during the first two hours of the eight-hour feeding period. In contrast, fenfluramine administration resulted in a more prolonged suppression in caloric intakes, with intakes significantly decreased below saline values throughout the feeding period. The differential effects of amphetamine and fenfluramine on temporal patterns of food intake are probably not simply due to differences in the time course of action of the two drugs. Blundell and colleagues [8] found that delaying access to food following fenfluramine injections did not alter the anorectic profile of the drug. That is, animals initiated feeding normally with a subsequent inhibition of food intake even when access to food was delayed for 30, 60 or 90 minutes after fenfluramine administration. These results led Blundell *et al.* [8] to suggest that a certain amount of food may have to be consumed for the inhibitory effect of fenfluramine to occur and that fenfluramine produces its inhibition of feeding by enhancing feedback

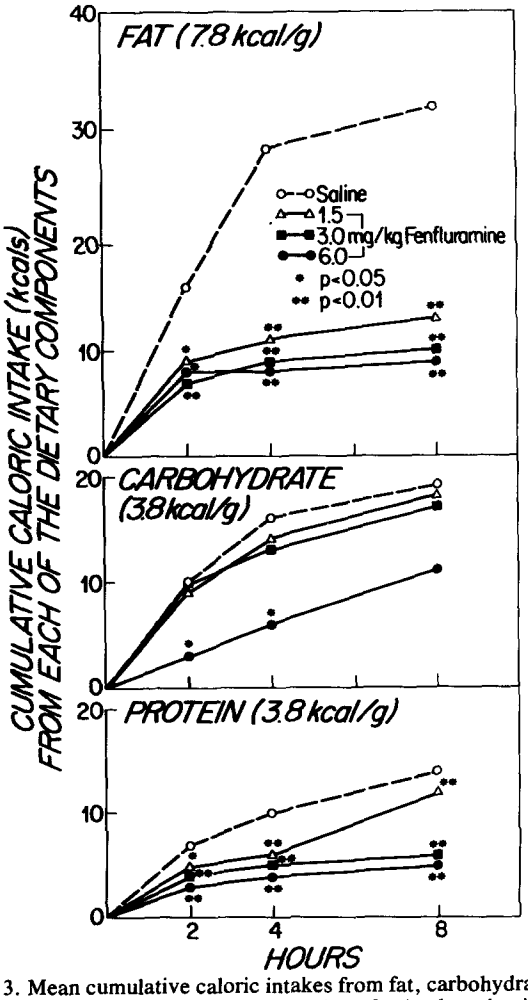

FIG. 3. Mean cumulative caloric intakes from fat, carbohydrate and protein across an eight-hour feeding period of animals maintained on a self-selection regime with a high-caloric fat ration following injections of saline, 1.5, 3.0 and 6.0 mg/kg fenfluramine. Significantly different from saline: *=$p<0.05$, **=$p<0.01$.

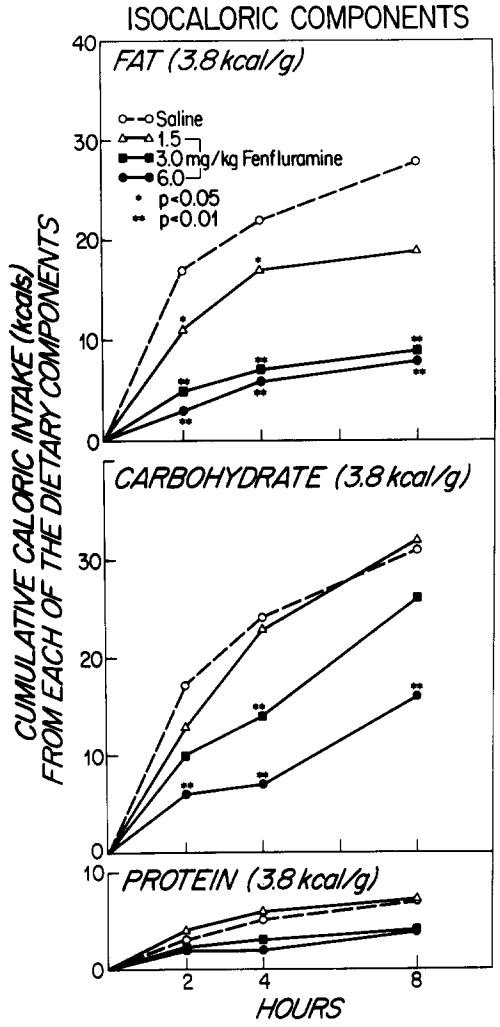

FIG. 4. Mean cumulative caloric intakes from fat, carbohydrate and protein across an eight-hour feeding period of animals maintained on a self-selection regime with isocaloric macronutrient components following injections of saline, 1.5, 3.0 and 6.0 mg/kg fenfluramine. Significantly different from saline: *=$p<0.05$; **=$p<0.01$.

signals from the consumption of food. The different temporal patterns of feeding behavior produced by amphetamine and fenfluramine clearly indicate the limitations of measuring food intake at only one time point following drug administration [7, 8, 10, 13, 15]. If, in the present experiment, food intake only had been measured at two-hours post-injection, it might be concluded that the two drugs produced rather similar anorectic effects. In contrast, if food intake had been measured at only eight-hours after drug administration, a greater anorectic potency for fenfluramine might be proposed.

In addition to producing different temporal patterns of feeding behavior, administration of amphetamine and fenfluramine led to rather different patterns of diet selection. Previous experiments also have reported differential effects of these two anorectic agents on nutrient choice [9, 24, 25]. In this earlier work, animals were provided with a choice between two isocaloric diets differing in the proportions of protein and carbohydrate they contained. Using this experimental paradigm, an elective decrease in carbohydrate intake with a sparing of protein intake was observed following fenfluramine administration for rats maintained on restricted feeding schedules [9, 24, 25]. In contrast, amphetamine administration, in this situation, led to relatively equivalent decreases in protein and carbohydrate intakes in animals maintained on restricted feeding schedules. On the basis of these results, it was hypothesized that modifications in neurotransmitter availability may be responsible for the patterns of nutrient choice observed following drug administration. More specifically, it was proposed that the protein sparing effect of fenfluramine was mediated through the increased availability of intrasynaptic serotonin resulting from drug administration [24]. Evidence for this proposal was provided by the observation that administration of other drugs, such as fluoxetine, which increase intrasynaptic levels of serotonin, also lead to selective decreases in carbohydrate consumption [24]. Additionally, recent research demonstrating that depletion of brain serotonin levels by systemic administration of para-chloro-phenyl-alanine, intraventricular injections of 5,7-dihydroxytryptamine or radiofrequency lesions of the midbrain raphe nuclei lead to a selective decrease in protein consumption [2] complement the preceding proposal.

The results of the present experiments, however, suggest that the relationship between neurotransmitter availability and diet selection are not as clear cut as one might wish. While in the present experiments, amphetamine and fenfluramine did differentially affect dietary self-selection, the pattern of nutrient choice (1) was rather different from that previously reported and (2) varied as a consequence of the composition of the dietary components. When animals were provided with a choice of separate sources of the three macronutrients including a high-caloric fat ration, amphetamine injections led to a sustained selective decrease in fat intake. Intakes of all three macronutrients were suppressed during the initial two hours of the feeding period. However, while both protein and carbohydrate intakes returned to control values by the end of the eight-hour feeding period, fat intake remained suppressed. When fenfluramine was given to animals maintained on the same self-selection regime (i.e., with the high-caloric fat ration), both fat and protein intakes were depressed throughout the feeding period, while carbohydrate intake was relatively unaffected. The effects of fenfluramine on diet selection, in this situation, are thus very different from those previously reported [9, 24,] 25]. A selective decrease in carbohydrate intake and a sparing of protein consumption was noted when animals were given a choice of two isocaloric diets varying in macronutrient composition [9, 24, 25]. In contrast, when animals were provided with separate sources of the macronutrients, fenfluramine administration led to a relative sparing of carbohydrate consumption and decreases in both protein and fat intakes.

Replacing the high-caloric fat ration with a fat ration isocaloric to the protein and carbohydrate rations led to substantial modifications in the effects of the two anorectic drugs on dietary self-selection. In contrast to the selective decrease in fat intake observed following amphetamine administration in animals given the high-caloric fat ration, a more general suppression in intakes of all three nutrients was noted after drug injections in animals given the isocaloric fat ration. For animals given the isocaloric components, intakes of all three nutrients were initially reduced and remained suppressed throughout the eight-hour feeding period following amphetamine administration. Providing animals with the

isocaloric fat ration, also altered the effects of fenfluramine on diet selection. When animals were given the isocaloric rations, fenfluramine adminstration actually led to a sustained decrease in fat intake and a relative sparing of both protein and carbohydrate consumption.

The present data in conjunction with previous work [9,15], clearly indicate the difficulties in trying to establish a one-to-one relationship between neurotransmitter availability and nutrient choice. Nutrient selection, itself, is influenced by a variety of factors including the age and sex of the animals tested, the exact composition of the macronutrient components, micronutrient availability and environmental conditions (e.g., temperature, feeding schedules) (for reviews see [1, 17, 19]). It, therefore, should not be surprising if these variables interact with pharmacological manipulations in determining patterns of nutrient selection. Patterns of dietary self-selection following amphetamine and fenfluramine administration, in fact, do vary as a function of feeding schedules. The protein-sparing effect of fenfluramine observed in food-restricted animals given a choice of two isocaloric diets was substantially diminished when animals were given ad lib access to food [9]. Additionally, in this situation, amphetamine resulted in only a slight decrease in percent protein intake in food-restricted animals and a striking reduction in percent protein intake in freely-feeding animals. While not yet tested, it may be assumed that modifications in other variables which influence nutrient choice could alter the effects of anorectic agents on dietary self-selection.

It has been assumed that the effects of amphetamine and fenfluramine on food intake and nutrient choice are mediated through alteration in the availability of specific brain neurotransmitters [3, 4, 5, 12, 14, 24, 25]. However, both drugs may act upon other neurotransmitter systems that those assumed to be the primary target systems. Additionally, both amphetamine and fenfluramine can directly influence peripheral metabolic pathways. Administration of fenfluramine alters both carbohydrate and lipid metabolism (for review see [21]). More specifically with regard to carbohydrate metabolism, fenfluramine significantly increases glucose uptake by muscle [11, 16, 18, 21] and produces hypoglycemia in man and other animals. With respect to lipid metabolism, fenfluramine leads to an elevation in plasma levels of free fatty acids, glycerol and ketone bodies and a decrease in triglyceride and total plasma lipid levels [18, 20, 21]. Additionally, high doses of fenfluramine can decrease intestinal absorption of triglycerides [18,21]. Amphetamine also increases plasma free fatty acid levels, utilization and leads to hypoglycemia [22]. It is possible that drug-induced alterations in nutrient choice may not only reflect changes in brain neurotransmitter levels, but also, modifications in peripheral metabolism.

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