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Effect of Amphetamine on Human Macronutrient Intake

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FOLTIN, R. W., T. H. KELLY AND M. W. FISCHMAN. *Effect of amphetamine on human macronutrient intake.* PHYSIOL BEHAV **58**(5) 899–907, 1995.—Six male subjects participated in a 15-day residential study examining the effects of amphetamine on macronutrient intake. During the first 11 days, carbohydrate intake was manipulated by providing lunch meals high (155 g) or low (25 g) in carbohydrate. Subjects received oral d-amphetamine (5, 10 mg/70 kg, BID) or placebo. Total daily caloric intake was similar under both lunch conditions (~ 3400 Kcal), but carbohydrate contributed more energy under the high-carbohydrate condition. Both doses of amphetamine decreased total caloric intake to ~ 2600 Kcal, by decreasing the number of eating bouts, without affecting macronutrient selection. During the last four days subjects received a higher daily dose of amphetamine (30 mg/70 kg in four doses) or placebo, and were allowed to self-select lunch. Although 30 mg amphetamine decreased intake of all macronutrients, the relative contribution of carbohydrate to total caloric intake was increased from 54% to 62%, while the contribution of fat was decreased from 32% to 26% and the contribution of protein was decreased from 14% to 12%. Thus, at a high dose, amphetamine altered the relative contribution of specific macronutrients to total caloric intake.

Amphetamine Fat Carbohydrate Protein Caloric intake Food intake
Compensation Humans Macronutrients

ALTHOUGH no longer used clinically to aid weight loss, amphetamine reliably decreases body weight of overweight patients (see 5 and 33 for reviews). The handful of studies that have measured food intake of humans under controlled laboratory conditions clearly show that acute amphetamine administration is effective in decreasing caloric intake during a single meal (3,23,30,32) or across multiple meals (2,16,18,19). We have previously reported that amphetamine (10 mg/70 kg, BID) significantly decreased, by 30%, 24-h caloric intake of volunteers who had access to a wide variety of standard foods while living in a residential laboratory (12).

The possibility that specific neurotransmitter activity may be linked to specific macronutrient intake has generated much experimental fervor (e.g., 6,7,25,31,36). The effects of amphetamine, presumedly mediated predominantly by increases in synaptic dopamine levels (24), on macronutrient intake in rats have been studied, but, the results have been mixed; selective decreases in protein (26,27) or fat intake (20), as well as no selective changes in macronutrient intake (29,35) have been reported. Blundell and Rogers (3) found that a single dose of amphetamine (10 mg) decreased protein and fat intake by humans within a single meal, without affecting total caloric intake. In the previous residential study from this laboratory (12), amphetamine decreased total daily intake of fat, carbohydrate and protein, but the relative contributions of each macronutrient to total daily caloric intake were not reported. Clearly the relationship between amphetamine and macronutrient intake remains obscure.

The purpose of the present study was to further investigate the possible effects of amphetamine on the macronutrient intake of volunteers living in a residential laboratory, who had access to a wide variety of foods with few restrictions on food consumption. This issue was addressed during the first 11 days of the study by administering total daily amphetamine doses of 10 mg and 20 mg under conditions in which macronutrient intake was manipulated by requiring subjects to consume lunch meals varying in carbohydrate content. Previous data from this laboratory indicate that

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daily macronutrient intake can be readily manipulated by varying macronutrient content of required eating occasions (13,14). In the present study, lunch meals varying in carbohydrate content were consumed on days when subjects also received placebo or active amphetamine to determine if increasing the contribution of carbohydrate to total caloric intake would modulate the anorectic effects of amphetamine. It was hypothesized that the anorectic effect of amphetamine would be independent of the macronutrient composition of the diet. During the last four days of the study, the effect of amphetamine on macronutrient intake was addressed by testing a larger total daily dose of amphetamine, 30 mg (in four doses), and allowing subjects to self-select lunch.

METHODS

Subjects

Two African-American and four NonHispanic Caucasian healthy adult male research volunteers ranging in age from 27 to 35 yr [29.7 ± 1.9 yr (mean ± SEM)], participated in 15-day experiments. All subjects were within accepted weight ranges [71.0 ± 3.4 kg, (Metropolitan Life Insurance Company, 1983)], had low dietary restraint [< 10, (34)], and had no self-reported eating abnormalities. Three of the six subjects reported smoking tobacco cigarettes (7, 20, and 20 per day), and continued to do so during the experiment. Subjects received complete medical and psychiatric evaluations, signed consent forms detailing all aspects of the research, and were paid for participation. Subjects were not informed prior to the study that they would be given amphetamine. They were instructed that they were participating in a study on the effects of a commonly used sedative or stimulant drug on the stability of computer performance over prolonged periods of time. They were, however, fully informed about drug conditions prior to discharge.

Laboratory

Subjects, in two groups of three, lived in a residential laboratory designed for continuous observation of human behavior over extended periods of time (4). The facility, which consisted of six rooms connected by a common corridor, was housed within a wing of The Johns Hopkins Hospital. Three identical rooms were similar to small efficiency apartments with kitchen, bathroom, desk and bed. A three-room social area consisted of a recreation room, an exercise room and a bathroom. The recreation room contained kitchen facilities, lounge furniture, a variety of games and puzzles, videogames, and a monitor for viewing video-taped movies. The recreation room also contained an electronic scale with a readout in the control room for the daily weighing of subjects. The exercise room contained exercise equipment (stationary bicycle, free-weights, etc.) and laundry facilities. Two-way cabinets in each room of the laboratory allowed for the transfer of items between subjects and experimenters without direct contact. Each private room had an Apple IIe® microcomputer located on the subject's desk, and a similar computer was located in the recreation area.

Output from a video and audio monitoring system terminated in an adjacent control room. Subjects were observed continuously except in private dressing areas and toilet facilities. Communication between subjects and experimenters was kept to a minimum, and was accomplished using a networked computer system, linking the computers in each room of the laboratory with the main control room (subjects did not have access to each other's computers). This communication system allowed for continuous on-line interaction between subjects and experimenters.

Standard Day

Subjects were awakened at 0900 by presenting a tone until the subject signaled that he was awake, and the day ended with lights out at 2400. Subjects were weighed each morning in stocking feet after voiding, but were not informed of their weight. At that time, a staff member met with each subject individually. Two to three hour work periods occurred each day: 1000–1300 and 1330–1630. During these periods, subjects were instructed to remain in their private rooms and engage in computerized "work" tasks. Subjects selected among four task options (21). The other options available during these periods were eating or using the bathroom. Work tasks were three-min in duration, and subjects were given a small bonus at the end of the study based on their performance during each work period (one to four dollars per period, or two to eight dollars per day). On days 3–10, at 1300, subjects were provided with a lunch meal in their private rooms and given 30-min to consume the entire meal. Subjects could supplement the planned lunch with other items contained in their snack boxes, or by requesting frozen food items. At 1330 subjects returned the empty lunch trays. Beginning at 1700, subjects had access to activities available in the social rooms. Two video-taped films were shown, beginning at 1840 and 2040. Clocks or watches were not permitted, but subjects were told the time via their computer at each activity transition (e.g., 0900, 1000, 1300, etc). With the exception of the first day, a drug beverage was administered at 0935, 1635, 1835, and 2035. Subjects were given five min to drink a 90-ml beverage in their private rooms, while under observation from the control room. Placebo beverages consisted of 90 ml of Welch's grape juice with 1 ml of 95% ethanol floated on top. On active drug days, d-amphetamine elixir (Dexedrine®, 1 mg/ml dextroamphetamine in a 10% ethanol solution; Smith, Kline & French, Philadelphia, PA) was added to yield drug doses adjusted for body weight. Pulses were obtained for the five-min prior to drug delivery via finger plethysmographs (Lafayette Instruments) with output to the control room. If heart rate was above 90 bpm, drug was not delivered.

Procedure

Subjects received one or two days of training on the computerized performance tasks until performance stabilized, and received 10 mg/70 kg *d*-amphetamine on an additional day prior to residence. Subjects reported to the laboratory on the day before the study, were oriented to living in the facility, received additional task training, and slept in the laboratory so that the first experimental day could begin at 0900 the following morning. Subjects were provided low-carbohydrate lunches in two-day blocks on days 3, 4 and 7, 8, and high-carbohydrate lunches in two-day blocks on days 5, 6 and 9, 10. No planned lunches were provided on all other days (i.e., subjects self-selected lunch). Placebo amphetamine was always administered on the first day, while active drug was given on the second day of each two-day lunch condition. Subjects in Group I received 5 mg/70 kg *d*-amphetamine (BID) on days 4 and 10, and 10 mg/70 kg *d*-amphetamine (BID) on days 6 and 8; dosing order was reversed for the subjects in Group II. On days 4, 6, 8, and 10, active drug was given at 0935 and 1635, and placebo was given at 1835 and 2035. Subjects received placebo QID on days 2, 3, 5, 7, 9, 11, 13 and 15. A 30 mg/70 kg total dose of *d*-amphetamine was administered on days 12 and 14: 10 mg/70 kg at 0935 and 1635, and 5 mg/70 kg at 1835 and 2035.

Food Monitoring

Food consumption was monitored. After weighing-in each morning, a box of food was placed in the food drawer of each of

the three private rooms. This box contained a variety of foods including meal items, conventional snacks, and beverages (see 13, 14, for a complete list of foods), which could be consumed at any time during the experimental day (0900–2300). Each snack portion size was designed to contain a roughly equivalent energy content (~ 125–175 Kcal). Subjects were free to request additional units of any items ad lib. Frozen meals were available by request throughout the experimental day. To facilitate choice of frozen meals, subjects were provided with a book containing package pictures of each item. In addition, subjects had access to instant coffee, tea and water at all times. Foods varied in macronutrient content to provide the opportunity for differential macronutrient intake across the study.

Subjects were told that their food intake was continuously monitored and were instructed to inform the research monitors via the computerized communication system whenever they ate or drank something, specifying substance and portion. Wrappers for each item were color-coded by subject to facilitate data collection. Trash was removed and examined daily to validate verbal reports and observer records of food intake, and to control for the possibility of food hoarding. Previous studies indicated that these procedures have no significant effect on total daily intake, and maintain behavior sensitive to manipulations affecting daily amount and patterning of food intake (9,12–14).

Planned Lunches

The planned lunch, consisting of a beverage, cold cuts, bread, mayonnaise and a gelatin dessert, contained 788 kcal under the high-carbohydrate condition, and 392 kcal under the low-carbohydrate condition, with the caloric differential derived predominantly from carbohydrate. Under the high-carbohydrate condition, lunch consisted of 475 g of a carbonated orange beverage (Minute Maid®), 125 g of turkey breast, three slices of bread (84 g, Roman Meal®), 20 g of reduced-calorie mayonnaise (Hellman's®) and 150 g of strawberry gelatin (Jell-o®). Under the low-carbohydrate lunch condition, reduced-calorie versions of the orange beverage, gelatin and bread (69 g, Schmidt's® "Less" heart bran) were substituted for the regular-calorie items, reducing carbohydrate content by 100 g, fat content by 3 g and protein content by 8 g, and total weight by 15 g. Subjects were given each item in a separate package and instructed to make a

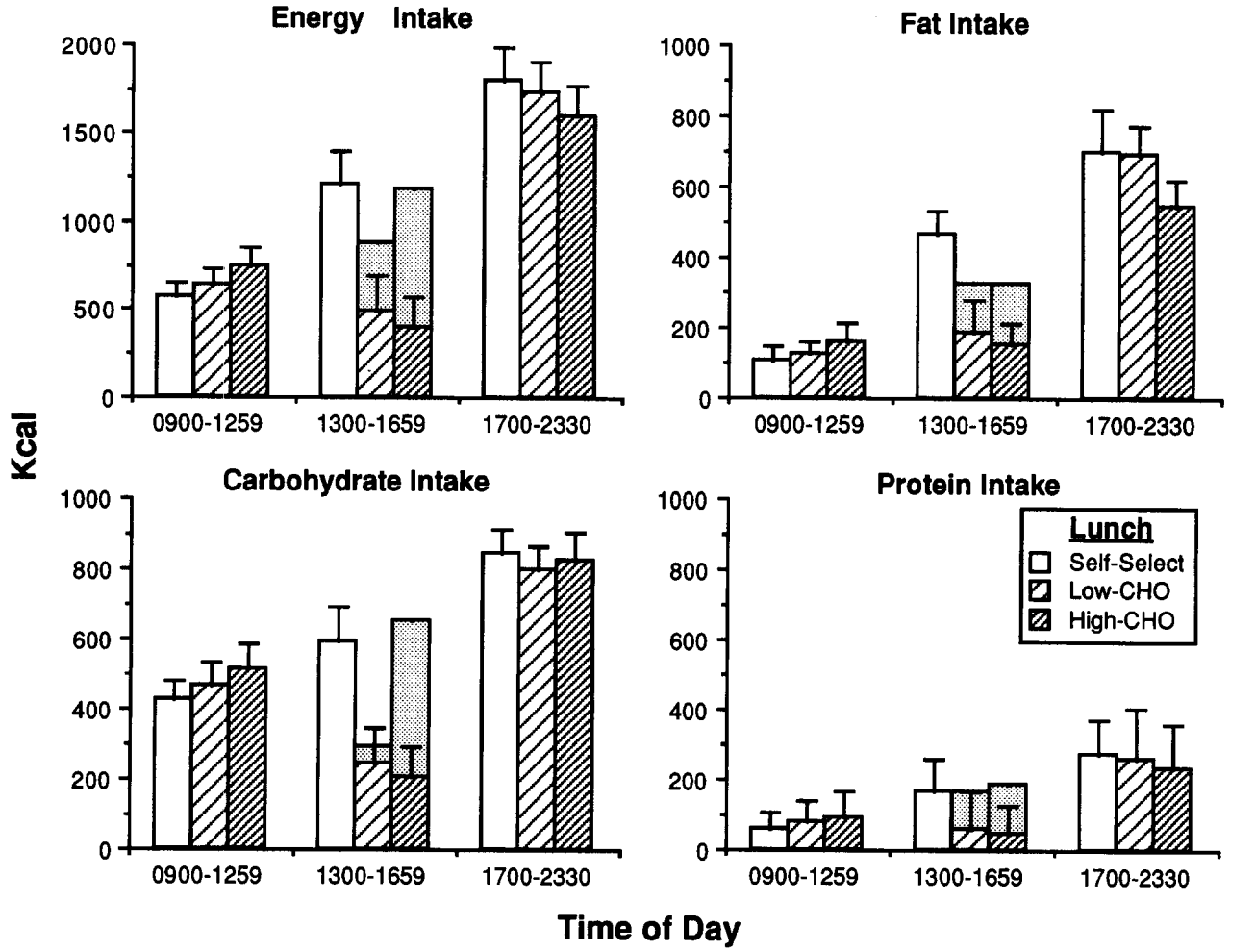

FIG. 1. Mean total caloric intake and caloric intake derived from carbohydrate, fat and protein (estimated from g intake using Atwater factors) as a function of time of day when subjects self-selected lunch or were provided a lunch low (Low-CHO) or high (High-CHO) in carbohydrate. Each data point represents the mean obtained under two days of each condition when subjects received placebo. Hatched bars at the 1300–1659 time point indicate intake without the content of the planned lunches, while the shaded area above each hatched bar represents intake including the content of the planned lunches. Error bars represent 1 SEM.

sandwich, or eat the items in any other manner, within 30 min. Uneaten food was returned to the subject for consumption.

Data Analysis

Data analyses addressed three issues. (i) How did consumption of planned lunches varying in carbohydrate affect food intake compared to the self-selected lunch baseline condition? (ii) Did the effects of amphetamine on food intake differ between the low- and high-carbohydrate lunch conditions? (iii) What were the effects of large total daily amphetamine dose on food intake? The first question was addressed using placebo data, including and excluding the planned lunches, collected on two self-selected lunch days (Day 2, 11), the two low-carbohydrate days and the two high-carbohydrate days. The second question was addressed using data, excluding the planned lunches, collected on the eight days that subjects consumed a planned lunch, and the third question was addressed using data obtained on the last four days of the study, when there were no planned lunches.

The data used in the analyses were based on the subjects' reports of food intake as verified by trash examination. Total energy intake, and energy intake of carbohydrate, fat, and protein [estimated as Kcal from g-intake using Atwater factors (28)] were summarized as a function of time of the day (0900–1259, 1300–1659, 1700–2330). Mean number of eating bouts, inter-bout-interval, total caloric intake, and caloric intake derived from fat, carbohydrate and protein were determined using a minimal inter-bout interval of ten min: a bout was defined as beginning with the first report of an item to be consumed and ending when there was a pause of greater than 10 min between food reports. Bout parameters and the percent of energy intake derived from each of the three macronutrients were analyzed based on data obtained for the entire day.

The analyses of the effects of planned lunches on food intake were accomplished using three-factor repeated measures analyses of variance: the first factor was lunch condition (self-select, low-carbohydrate, high- carbohydrate), the second factor was test day (first or second), and the third factor was time of day (0900–1259, 1300–1659, 1700–2330). Due to the differential occurrence of planned lunches across the conditions, no analyses of bout parameters were attempted. The analyses of the effects of planned lunches on changes in food intake following amphetamine administration were accomplished using four-factor repeated measures analyses of variance: the first factor was lunch carbohydrate content (low, high), the second factor was drug (amphetamine or placebo), the third factor was dose and the fourth factor was time of day. The effects of a large total daily amphetamine dose was accomplished using using three-factor repeated measures analyses of variance: the first factor was drug (30 mg amphetamine or placebo), the second factor was test day (first or second), and the third factor was time of day. Results were considered statistically significant if $p < 0.05$ using Hunyh-Feldt corrections. The probability values for nonsignificant results will also be presented to provide a better indicator of possible patterns in the data.

RESULTS

Effect of Planned Lunches on Food Intake

Figure 1 compares mean caloric and macronutrient intake in the morning, afternoon and evening on drug-free days when subjects either self-selected lunch or consumed the low-or high-carbohydrate lunches. Data graphed for the middle of the day (1300–1659) include intake without planned lunches (hatched bars) and intake with planned lunches (stippled bars). Caloric intake (upper left panel) increased across the day from about 500 Kcal in the morning to about 1700 Kcal in the evening [$F(2, 10) = 8.12$, $p < 0.026$]. There were significant interactions between lunch condition and time of day when lunch was [$F(4, 20) = 3.24$, $p < 0.033$], or was not included in the analyses [$F(4, 20) = 11.29$, $p < 0.001$], with the largest effects occurring in the middle of the day. Although energy derived from carbohydrate (lower left panel) increased across the day from about 400 Kcal in the morning to about 800 Kcal in the evening, this effect did not reach significance ($p < 0.061$). There were significant interactions between lunch condition and time of day when lunch was [$F(4, 20) = 7.25$, $p < 0.009$], or was not included in the analyses [$F(4, 20) = 10.93$, $p < 0.001$], with the smallest carbohydrate intake clearly occurring in the middle of the day when subjects consumed the low-carbohydrate lunch. Energy derived from fat (upper right panel) increased across the day from about 100 Kcal in the morning to about 700 Kcal in the evening [$F(2, 10) = 9.01$, $p < 0.013$]. There was only a significant interaction between lunch condition and time of day when lunch was not included in the analyses [$F(4, 20) = 6.55$, $p < 0.002$]. Finally, energy de-

TABLE 1

PERCENTAGE CONTRIBUTION OF EACH MACRONUTRIENT TO TOTAL DAILY CALORIC INTAKE

Macronutrient	Low-CHO*	High-CHO	Self-Select	p†
Planned Lunch Included (Placebo Administered)				
Carbohydrate	49.1 ± 1.5‡	56.7 ± 2.1	51.1 ± 1.7	0.002
Fat	35.2 ± 1.1	28.8 ± 1.6	35.0 ± 1.4	0.004
Protein	15.7 ± 0.7	14.5 ± 0.8	13.9 ± 0.9	0.006
Planned Lunch Excluded (Placebo Administered)				
Carbohydrate	53.0 ± 2.0	56.2 ± 2.7	51.1 ± 1.7	0.096
Fat	33.7 ± 1.4	30.6 ± 2.0	35.0 ± 1.4	0.116
Protein	13.3 ± 0.9	13.1 ± 1.0	13.9 ± 0.9	0.355
10–20 mg/70 kg *d*-Amphetamine Daily Dose (Planned Lunch Excluded)				
Macronutrient	Amphetamine		Placebo	*p*
Carbohydrate	55.6 ± 2.0		54.6 ± 1.7	0.729
Fat	32.2 ± 1.5		32.2 ± 1.2	0.995
Protein	12.2 ± 0.9		13.2 ± 0.8	0.188
30 mg/70 kg *d*-Amphetamine Daily Dose				
Carbohydrate	62.3 ± 2.5		53.6 ± 2.7	0.004
Fat	25.7 ± 1.8		32.1 ± 1.9	0.004
Protein	12.0 ± 1.3		14.3 ± 1.3	0.035

* CHO – Carbohydrate; † Significance of differences among the two or three conditions; ‡ Mean ± SEM.

rived from protein (lower right panel) increased across the day from about 50 Kcal in the morning to about 200 Kcal in the evening [$F(2, 10) = 9.18$, $p < 0.010$], and, as with the other macronutrients there was a significant interaction between lunch condition and time of day when lunch was not included in the analyses [$F(4, 20) = 6.30$, $p < 0.003$].

Another way to evaluate macronutrient intake is to examine the percentage of total daily caloric intake derived from each macronutrient. The top half of Table 1 compares the percentage of total daily energy intake derived from each macronutrient on the self-selected lunch days, and days when subjects consumed the low- or high-carbohydrate lunches and received placebo. Under the self-selected lunch condition, subjects derived about 51% of their energy intake from carbohydrate, 35% from fat and 14% from protein. Changing the carbohydrate content of lunch significantly altered macronutrient contribution to total daily intake. Consumption of the high-carbohydrate lunch increased the contribution of carbohydrate [$F(2, 10) = 11.59$], and decreased the contribution of fat to total caloric intake compared to the other lunch conditions [$F(2, 10) = 9.82$]. Consumption of the low-carbohydrate lunch significantly increased the contribution of protein to total caloric intake compared to the other lunch conditions [$F(2, 10) = 9.75$]. When the macronutrient content of lunch was not include in the analyses, the contribution of each macronutrient to total daily caloric intake did not differ significantly among the three lunch conditions. Thus, consumption of the high-carbohydrate lunch increased the contribution of carbohydrate and decreased the contribution of fat and protein to total daily caloric intake compared to the low-carbohydrate lunch condition, without affecting total daily caloric intake.

Interaction of Amphetamine with Lunches Varying in Carbohydrate

Figure 2 compares mean caloric and macronutrient intake in the morning, afternoon and evening on days when subjects consumed the low-or high-carbohydrate lunches and received placebo or active amphetamine. The caloric and macronutrient content of the planned lunches were not included in the statistical analyses. While amphetamine significantly decreased caloric intake [upper left panel; $F(1, 5) = 11.92$, $p < 0.018$], and intake increased across the day [$F(2, 10) = 9.71$, $p < 0.016$], there was also a significant interaction between drug administration and time of day [$F(2, 10) = 4.37$, $p < 0.043$], with amphetamine decreasing caloric intake predominantly after 1700 (i.e., "PM" on the Fig. 2). There were no dose-dependent effects of am-

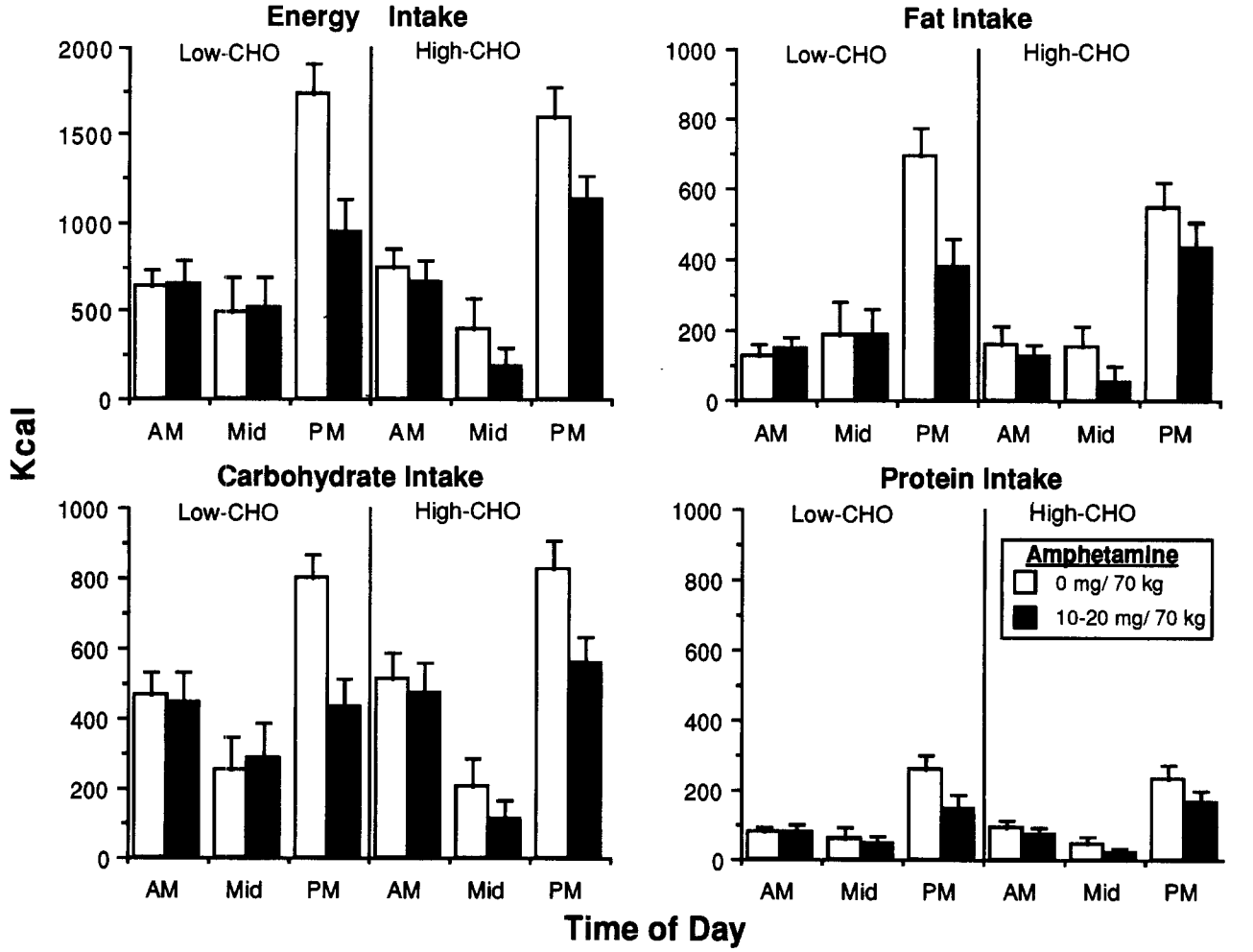

FIG. 2. Mean total caloric intake and caloric intake derived from carbohydrate, fat and protein (estimated from g intake using Atwater factors) as a function of time of day (AM:0900–1259; Mid:1300–1659; PM:1700–2330) when subjects received placebo or 10–20 mg/70 kg amphetamine and were provided a lunch low (Low-CHO) or high (High-CHO) in carbohydrate. Data presented at the 1300–1659 time point indicate intake without the content of the planned lunches. Error bars represent 1 SEM.

TABLE 2
EATING BOUT PARAMETERS UNDER AMPHETAMINE AND PLACEBO CONDITIONS

Measure	Amphetamine	Placebo	p*
10–20 mg/70 kg *d*-Amphetamine Daily Dose (Planned Lunch Excluded)			
Number of Bouts	3.7 ± 0.3†	5.0 ± 0.4	0.001
Inter-Bout-Interval (min)	225.8 ± 22.1	174.2 ± 16.8	0.003
Kcal	653.0 ± 68.8	625.1 ± 53.1	0.344
Carbohydrate (Kcal)	368.7 ± 40.4	342.5 ± 29.3	0.253
Fat (Kcal)	216.6 ± 25.6	207.7 ± 20.5	0.617
Protein (Kcal)	83.0 ± 9.9	86.7 ± 8.4	0.337
30 mg/70 kg *d*-Amphetamine Daily Dose			
Number of Bouts	4.7 ± 0.5	5.3 ± 0.5	0.058
Inter-Bout-Interval (min)	231.2 ± 36.7	220.4 ± 42.9	0.483
Kcal	525.1 ± 77.1	584.2 ± 66.5	0.105
Carbohydrate (Kcal)	327.2 ± 23.6	317.4 ± 25.9	0.541
Fat (Kcal)	142.8 ± 46.8	193.0 ± 37.9	0.031
Protein (Kcal)	65.5 ± 11.3	86.4 ± 11.6	0.055

* Significance of difference between amphetamine and placebo; † Mean ± SEM.

phetamine in any analysis. The effect of amphetamine on caloric intake was independent of the carbohydrate content of lunch ($p < 0.986$; lunch × drug interaction). Amphetamine decreased food intake in the afternoon under the high-carbohydrate lunch condition to a greater extent than under the low-carbohydrate condition, but this effect was not significant ($p < 0.251$).

Amphetamine significantly decreased carbohydrate intake [lower left panel; $F(1, 5) = 24.71$, $p < 0.004$], and carbohydrate

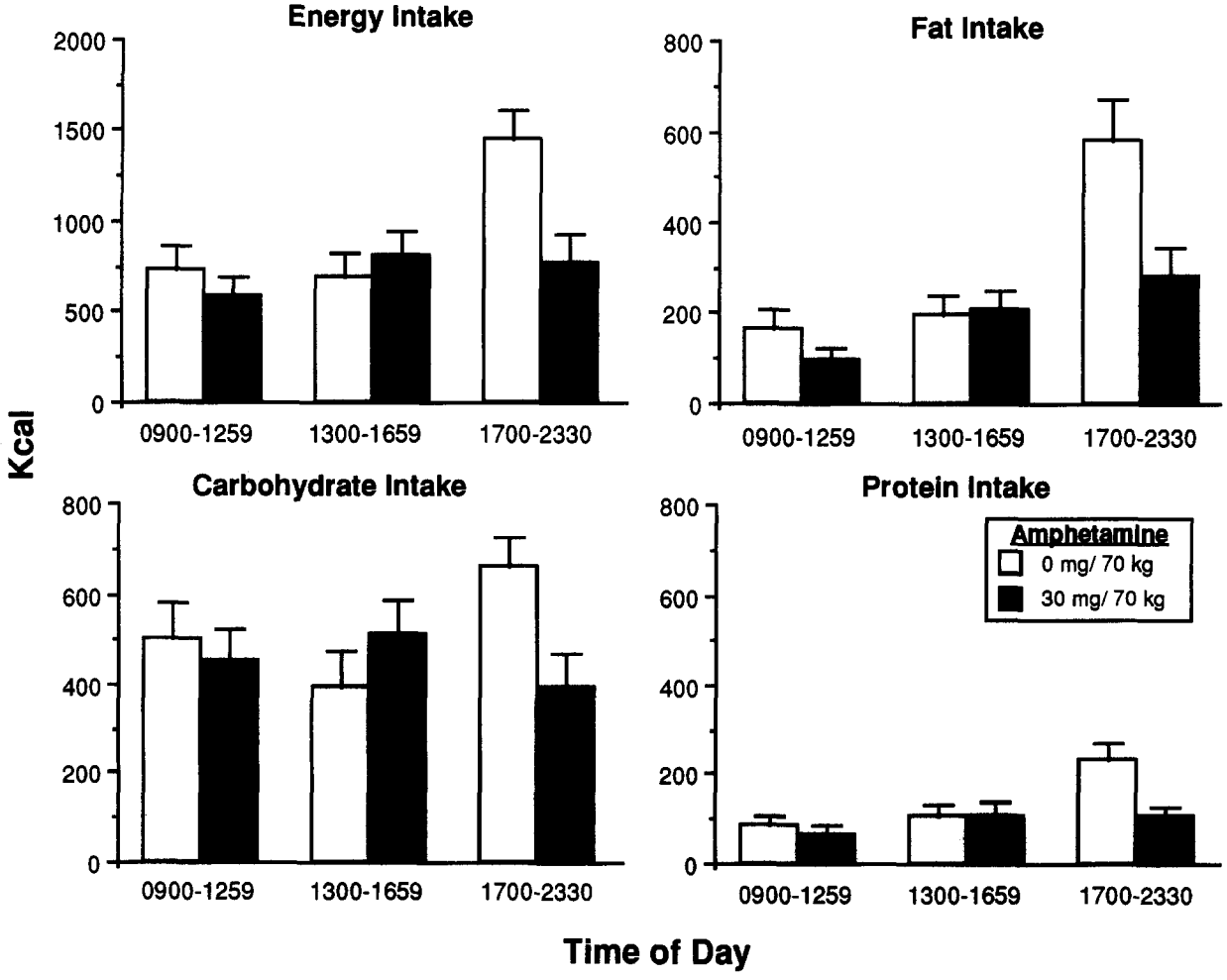

FIG. 3. Mean total caloric intake and caloric intake derived from carbohydrate, fat and protein (estimated from g intake using Atwater factors) as a function of time of day when subjects received placebo or 30 mg/70 kg amphetamine during the last four days of the experiment. Subjects self-selected lunch on these days. Error bars represent 1 SEM.

intake increased across the day [$F(2, 10) = 8.89$, $p < 0.001$]. The interaction between drug administration and time of day, however, failed to reach significance ($p < 0.059$). The effect of amphetamine on carbohydrate intake was independent of the carbohydrate content of lunch ($p < 0.697$). Although, amphetamine appeared to decrease fat consumption (upper right panel), this effect was not significant ($p < 0.083$), and there was no significant interaction between drug administration and time of day ($p < 0.128$). Fat intake did increase across the day [$F(2, 10) = 9.64$, $p < 0.019$]. While amphetamine significantly decreased protein intake [lower right panel; $F(1, 5) = 11.65$, $p < 0.019$], and intake increased across the day [$F(2, 10) = 8.75$, $p < 0.019$], there was also a significant interaction between drug administration and time of day [$F(2, 10) = 5.68$, $p < 0.022$], with amphetamine decreasing protein intake predominantly after 1700. The effect of amphetamine on protein intake was independent of the carbohydrate content of lunch ($p < 0.922$). Amphetamine in doses of 10-20 mg/70 kg had no significant effect on the contribution of each macronutrient to total daily caloric intake (Table 1).

The top portion of Table 2 compares the parameters describing eating bouts on days when subjects consumed planned lunches varying in carbohydrate content and received placebo or active amphetamine. As there were no significant effects of dose or carbohydrate content of lunch on any measure, data are averaged across the 10–20 mg/70 kg doses and both lunch conditions. Amphetamine significantly decreased the number of eating bouts [$F(1, 5) = 41.67$] by increasing the mean interval between bouts [$F(1, 5) = 30.45$]. Amphetamine had no significant effects on the energy or macronutrient content of the average eating bout. Thus, a daily dose of 10 – 20 mg/70 kg of amphetamine decreased food intake regardless of the carbohydrate content of meals by decreasing the number, but not size, of eating bouts.

30 mg Total Daily Dose of Amphetamine

Figure 3 compares caloric and macronutrient intake in the morning, afternoon and evening when subjects received placebo (i.e., days 13, 15) and 30 mg/70 kg amphetamine (i.e., days 12, 14), in divided doses. While amphetamine significantly decreased caloric intake [upper left panel; $F(1, 5) = 67.36$, $p < 0.001$], there was also a significant interaction between drug administration and time of day [$F(2, 10) = 14.73$, $p < 0.001$], such that amphetamine decreased caloric intake only after 1700. There was no main effect of amphetamine on carbohydrate intake (lower left panel; $p < 0.078$), but a significant interaction between drug administration and time of day indicated that amphetamine decreased carbohydrate intake only after 1700 [$F(2, 10) = 9.97$, $p < 0.0042$]. As described for caloric intake, amphetamine significantly decreased fat intake [upper right panel; $F(1, 5) = 136.00$, $p < 0.001$], and there was also a significant interaction between drug administration and time of day [$F(2, 10) = 12.37$, $p < 0.002$], such that amphetamine decreased fat intake predominantly after 1700. Although amphetamine decreased fat intake in the morning, this effect was not significant ($p < 0.167$). Amphetamine significantly decreased protein intake [lower right panel; $F(1, 5) = 41.22$, $p < 0.001$], and there was a significant interaction between drug administration and time of day [$F(2, 10) = 12.88$, $p < 0.003$], such that amphetamine decreased protein intake predominantly after 1700. In summary, 30 mg /70 kg amphetamine decreased total caloric intake by 24%, but only decreased total carbohydrate intake by 13%. In contrast, total fat intake was decreased by 39% and total protein intake was decreased by 35%. In contrast to the results obtained when subjects received 10 – 20 mg/70 kg amphetamine, 30 mg/70 kg amphetamine significantly altered the contribution of each macronutrient to total daily caloric intake. As shown in the bottom portion of Table 1, 30 mg/70 kg amphetamine administration significantly increased the contribution of carbohydrate [$F(1, 5) = 25.09$], and decreased the contribution of fat [$F(1, 5) = 24.1$] and protein [$F(1, 5) = 8.23$] to total daily caloric intake.

As shown in the bottom portion of Table 2, 30 mg/70 amphetamine also affected bout parameters differently than the lower doses of amphetamine. Amphetamine slightly, but not significantly decreased the number of eating bouts and decreased the fat [$F(1, 5) = 8.83$] and protein [$F(1, 5) = 6.23$] content of bouts.

DISCUSSION

The acute administration of amphetamine (10–30 mg/70 kg total daily dose) decreased total daily caloric intake of healthy male volunteers by 24–30%, extending previous findings based on 24-h food intake (12,16,19). There were no significant differences between the effects of 10 and 20 mg/70 kg in the first part of the study. Dose-dependent differences may have been obtained if subjects had not been required to consume planned lunches each day. The 30 mg daily dose actually produced a smaller percent change in caloric intake, but intake under placebo conditions was lower at the end of the study compared to the beginning. These results suggest that the maximal effects of amphetamine on food intake can be obtained with a relatively low acute dose.

One purpose of this study was to examine the possible effects of amphetamine on macronutrient intake when volunteers had access to a wide variety of standard foods, under conditions providing varied levels of macronutrient intake. In this study, macronutrient contributions to total daily caloric intake were manipulated by requiring subjects to consume lunch meals varying in carbohydrate content with matched fat and protein content. As previously reported (13), the consumption of a high-carbohydrate lunch increased the contribution of carbohydrate and decreased the contribution of fat to total daily intake. Amphetamine similarly decreased daily caloric intake independent of the carbohydrate content of the lunch. These results confirm the hypothesis that the anorectic effects of amphetamine were independent of baseline levels of macronutrient intake.

When the caloric and macronutrient content of the lunch were not included in the analyses, the relative contribution of each macronutrient to remaining caloric intake was unchanged from the self-selected lunch condition. Consumption of varying amounts of carbohydrate at lunch did not affect carbohydrate intake later in the day (13,14). Amphetamine (10 – 20 mg/70 kg) decreased the consumption of all three macronutrients, and there were no differences in the relative contribution of each macronutrient to total daily intake compared to the placebo days under the same lunch condition. Amphetamine decreased fat intake by about one third, and carbohydrate and protein intake by about one fourth.

Amphetamine did, however, significantly alter the contribution of macronutrients to total daily intake when lunch was self-selected and subjects received a 30 mg/70 kg total daily dose. Although 30 mg amphetamine significantly decreased the consumption of all three macronutrients, the smallest relative decrease was in carbohydrate and the largest relative decreases were in fat and protein consumption. Regardless of the fact that 30 mg amphetamine decreased total caloric intake, the relative contribution of carbohydrate to total caloric intake was significantly increased, while contribution of fat and protein was de-

creased. Thus, amphetamine had a relative carbohydrate-sparing effect.

We have previously reported that there were no differential effects of amphetamine on macronutrient intake (12). Although that study did not report on the relative macronutrient contribution to total daily intake, a retrospective analysis of the data confirmed that macronutrient contribution was unaffected by 10 mg of amphetamine given twice daily: carbohydrate—61%, fat —29%, and protein—9%. The data obtained during the first 11 days of this study corroborate that amphetamine, in doses up to 20 mg/70 kg per day, does not affect macronutrient choice (also see 17). An effect of amphetamine on macronutrient selection was only observed under the 30 mg dose condition. The findings obtained under the 30 mg condition parallel a trend described by Blundell and Rogers (3, 30). They provided adult volunteers, who were 17 h food-deprived, a lunch of bread, butter and sliced beef and ham 3 h after administration of 10 mg amphetamine. Although amphetamine had no effect on total caloric intake, fat and protein intake was reduced, increasing the relative contribution of carbohydrate to total meal intake.

While some reports have suggested that amphetamine specifically reduces protein intake in rats (26, 27), the effects of amphetamine on macronutrient intake of laboratory animals are varied (15,20,29,35). The effects of amphetamine on macronutrient selection are quite sensitive to experimental procedures. For example, Kanarek (20) reported that amphetamine produced prolonged decreases in fat consumption by rats maintained on a self-selection diet. In a later study (29), amphetamine also decreased fat intake of rats maintained on a high-fat diet, but amphetamine had no macronutrient-specific effects in rats maintained on an isocaloric diet. These findings suggest that amphetamine reduces the weight/volume of food consumed. Since the caloric density of fat ($\sim$ 9 kcal/gm) is greater than that of protein or carbohydrate ($\sim$ 4 kcal/gm), similar decreases in weight consumed would necessarily produce a greater effect on caloric intake derived from fat.

Clearly, given the mixed-macronutrient content of much of the human diet, studies on specific macronutrient intake can be difficult and open to procedural questions. The present results demonstrate that specific changes in macronutrient consumption can be observed in volunteers living in a residential laboratory given access to a wide variety of foods. Despite the limitations on activities and foods available compared to the natural ecology, the present laboratory conditions more closely approximate the natural ecology than those used in shorter-term studies.

The time-course data indicate that the largest effect of amphetamine occurred in the evening (1700–2330), replicating an earlier study (12). The absence of an effect in the morning could be explained by the fact that most morning food intake occurred during breakfast prior to amphetamine administration. The minimal effect of 10 – 20 mg/70 kg amphetamine on food intake during the afternoon could be due to the required consumption of the planned lunches. Lunches were self-selected when subjects received 30 mg amphetamine, however, such that the minimal effect of that dose on afternoon food intake could not have been a function of required lunch intake. Although subjects could eat during the morning and afternoon 3-h work periods, food consumption during these periods was low, often only consisting of water, tea or coffee drinking. These conditions are similar to the natural ecology, and it is unlikely that work performance blocked the effect of amphetamine.

The greater effect of amphetamine in the evening may be due to the higher baseline food intake during the evening, some aspect of the social situation such as less experimenter-imposed structure, or accumulating blood levels. The latter possibility is slim as the effects of amphetamine were not dose-dependent. It is also unlikely that food intake was due to toxic behavioral effects. Although not reported, the behavioral effects of amphetamine on performance and social behavior were similar to those already reported (11,22): amphetamine improved performance on some tasks and increased verbal interactions. There was no evidence that amphetamine, in this dose range, decreased food intake as a result of nonspecific behavioral disruptions.

The effects of amphetamine on multiple measures of feeding topography were also determined. The lower doses of amphetamine decreased food intake by decreasing the number of eating bouts and increasing the interval between bouts without affecting bout caloric or macronutrient content, replicating a previous study from this laboratory (12). Changes in eating bout parameters were more variable when subjects received 30 mg/70 kg amphetamine: a borderline significant decrease in bout number, and significant decreases in fat and protein content. The differences among amphetamine doses may be due to (i) the effects of the larger amphetamine dose; (ii) the fact that half as many test days were used in the analyses; or (iii) the fact that lunch meal was not included in the analyses of the effects of the lower doses. Variable results have also been obtained in studies using laboratory animals. In free-feeding rats, amphetamine increased latency to the first meal, decreased meal size and duration without affecting meal frequency (1,2,26). In contrast, amphetamine increased latency to the first meal, and decreased first meal size and number of meals, while fenfluramine decreased the number of meals in free-feeding baboons (8,10).

Amphetamine decreased food intake of humans living in a residential laboratory predominantly by decreasing eating in the evening. The effect of amphetamine on total daily caloric intake was not dose-dependent, but there were some differences between low and high doses in measures of feeding topography and macronutrient intake.

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