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Food Intake in Baboons: Effects of *d*-Amphetamine and Fenfluramine

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FOLTIN, R. W. AND M. W. FISCHMAN. *Food intake in baboons: Effects of* d-*amphetamine and fenfluramine.* PHARMACOL BIOCHEM BEHAV **31**(3) 585–592, 1988.—Food intake of four adult male baboons (*Papio c. anubis*) was monitored during daily experimental sessions lasting 22 hours. Food was available under a two-component operant schedule. Following completion of the first "procurement component" response requirement, access to food, i.e., a meal, became available under the second "consumption component" during which each response produced a one-g food pellet. After a 10-minute interval in which no response occurred, the consumption component was terminated. The effects of oral *d*-amphetamine (AMPH: 0.03–1.0 mg/kg) and fenfluramine (FEN: 0.25–2.0 mg/kg) were determined by having the baboons drink a dose on Tuesdays and Fridays 45 to 60 min before the daily session. Dose-dependent decreases in food intake were observed with AMPH being four times as potent as FEN. Although both drugs were equally efficacious in decreasing food intake, they had dissimilar effects on the topography of feeding behavior. AMPH decreased food intake by increasing the latency to the first meal, decreasing the size of the first meal, and decreasing the number of meals within a session. FEN, in contrast, had no significant effect on latency to the first meal or size of the first meal, but decreased the number of meals within a session. In addition, the drugs had different effects on the patterning of responding within the first meal. Finally, at the doses tested, there was no evidence of nonspecific motor deficits disrupting food intake. Although there are some differences between these results and the previously reported effects of these drugs, it is clear that AMPH and FEN influence feeding behavior in different ways.

Feeding behavior Meal patterns Free-feeding Baboons Amphetamine Fenfluramine Anorectic drugs

EXPERIMENTAL evidence supports the hypothesis that drugs which alter dopaminergic systems affect feeding behavior differently than drugs which alter serotonergic systems [e.g., (1, 3, 20)]. The majority of previous research has compared the anorectic effects of *d*-amphetamine (AMPH), presumably mediated by the release of catecholamines, particularly dopamine (19), and the anorectic effects of fenfluramine (FEN), presumably mediated by the release of serotonin (15). The difference in neurochemical mechanism of action is reflected by differences in the behavioral effects of these compounds. In free-feeding rats, AMPH increases latency to the first meal, decreases meal size and duration, produces dose-dependent increases in eating rate, and decreases or has no effect on meal frequency [e.g., (3, 4, 21)]. In contrast, FEN has no effect on latency to initiate feeding or meal frequency, but decreases meal size, duration and rate of eating [e.g., (3, 4, 24)].

In spite of the widespread clinical use of these compounds in humans (11,25), there has been little research on the effects of these drugs in nonhuman primates. Only four previous studies (9, 14, 16, 26) have systematically evaluated the effects of anorectic drugs on food intake in nonhuman primates. However, in three of these experiments (9, 14, 26), food intake was limited to a single short (one- to two-hr) daily session. Under these conditions, animals are insensitive to manipulations affecting the initiation of feeding (8). In the remaining experiment (16), baboons had continuous access to food under conditions requiring responding on one manipulandum, while responding on an alternate manipulandum resulted in intravenous infusions of anorectic drugs. Drug was available eight times a day. This procedure related total daily dose to food intake, but did not provide information about patterning food intake following acute drug delivery. Thus, although both AMPH and FEN produced dose-dependent decreases in food intake, differences in their effects on feeding topography have not been evaluated in nonhuman primates. The purpose of the present research was to evaluate the species generality of the proposed differences in action of AMPH and FEN by determining the effects of these drugs in free-feeding baboons.

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METHOD

Animals and Apparatus

Four adult male baboons (*Papio cynocephalus anubis*), ranging in weight from 25.0 to 36.4 kg, were housed in standard primate cages (approximately 0.94×1.21×1.52 m high for the three larger baboons, and 0.82×0.94×1.2 m high for the smallest baboon). The light-dark cycle was provided by natural light. Chewable vitamins (Goldline, Ft. Lauderdale, FL) and a piece of fresh fruit (80–100 kcal) were given daily. Water was available ad lib. Due to the necessity of sedating baboons in order to determine body weight, animals were weighed only at the start and end of the experiment. Attached to the front of each cage was a panel consisting of a food hopper, two stimulus lights, a Lindsley lever (Gerbrands, Arlington, MA), and a pellet dispenser (BRS-LVE model PDC-005, Beltsville, MD). All schedule contingencies were programmed using an Apple IIe computer located in an adjacent room.

Feeding Schedule

Food was available 22 hours/day, 11:00 a.m.–9:00 a.m. the following morning. The remaining two hours of the day were used for cage and animal maintenance. Illumination of a red stimulus light indicated the availability of the initial component of the two-component schedule of food delivery. This "procurement component" required completion of a fixed number of responses. Upon completion of the ratio requirement, the red stimulus light was extinguished, and a green stimulus light was illuminated to indicate the availability of the second component of the food delivery schedule. During this "consumption component," each lever pull resulted in the delivery of a single one g banana-flavored pellet (3.1 kcal/g, Bio-Serv, Frenchtown, NJ) into the food hopper. After a ten-minute interval in which no responses occurred, the consumption component was terminated, the green light extinguished, and the red light illuminated. All pellets earned during each consumption component were defined as occurring within a single meal. In order to gain access to another meal, the baboon was required to complete the ratio requirement of the procurement component again. Initially, 10 responses on the lever were required to complete the ratio requirement of the procurement component (FR10:FR1). This response requirement was in effect until responding stabilized (less than 10% variation in the number of meals and less than 20% variation in food intake for three consecutive days). The procurement component response requirement was then systematically increased for each baboon until the number of meals stabilized between two and three per session. This resulted in different procurement response requirements among baboons: the response requirement was 100 responses for R-82, 200 responses for A-33, and 400 responses for both V-3 and Z-26. Although differences in response requirements were required to equate meal numbers across baboons, these procedures engendered similar patterns, intermeal-intervals and intake during meals across baboons (12).

Procedure

The effects of oral *d*-amphetamine sulfate (0.03–1.0 mg/kg, Sigma Chemical Corp., St. Louis, MO) and fenfluramine hydrochloride (0.25–2.0 mg/kg, Sigma Chemical Corp.) administered 45–60 min prior to the start of the daily session were determined in all baboons. The variability in the timing of dosing was due to the variability among baboons in the rate of consumption of the drug-containing fluid, which ranged from two to 15 minutes. The 45–60 min pretreatment time was chosen based on previous studies on the effects of these drugs on food intake when given orally to food-deprived rhesus monkeys (9, 14, 26). Doses were administered on Tuesdays and Fridays, assuming that food intake on the previous two days was stable. Drug was suspended in 75 ml of a dilute orange flavored (Tang®, General Foods Co., White Plains, NY, 90 kcal) or fruit punch flavored (Giant®, Giant Foods Co., Washington, DC, 45 kcal) solution. Throughout the experiment, on Mondays, Wednesdays and Thursdays, baboons were occasionally given the flavored solutions without any drug. Dose-response functions for AMPH were determined first in two baboons, while dose-response functions for FEN were determined first in the other two baboons. No two baboons received the same order of doses of ether AMPH or FEN.

Data Analysis

Response rate and interresponse times (IRTs) were recorded during both procurement and consumption components. Interresponse times for the procurement component were summarized in 5 1.0 sec bins with an additional bin for IRTs >5 sec. Responses during each quarter of the consumption component were summarized in 5 2.0 sec bins with an additional bin for IRTs >10 sec. Thus, it was possible to compare pattern of IRTs as a function of the quarter of a meal. Data analysis was accomplished using linear regression (Systat Inc., Evanston, IL). Effects were considered statistically significant if $p<0.05$.

RESULTS

Mean pellet intake for the three sessions prior to the start of the determination of the AMPH dose-response function was 475.0±36.3 g (mean with SEM) for V-3, 288.3±26.6 g for R-82, 504.5±25.5 g for Z-26 and 331.7±17.9 g for A-33, while mean pellet intake for the three sessions prior to the start of the determination of the FEN dose-response function was 363.3±76.6 g for V-3, 250.7±21.8 g for R-82, 504.3±41.2 g for Z-26, and 400.0±52.3 g for A-33. Figure 1 compares pellet intake, expressed as percent of baseline, during the first eight hours, i.e., the approximate daylight hours (top panel), and the entire 22 hours (bottom panel) of the daily session following AMPH and FEN. AMPH produced dose-dependent decreases in eight-hr intake, $t(21)=-4.70$, $p<0.001$, with a dose of 0.12 mg/kg decreasing intake to 50% of baseline. FEN significantly decreased eight-hr intake, $t(16)=-1.70$, p (one-tail) <0.054, with a dose of 0.50–1.0 mg/kg decreasing intake to 50% of baseline. Both AMPH $t(21)=-4.00$, $p<0.001$, and FEN, $t(16)=-3.23$, $p<0.005$, produced dose-dependent decreases in 22-hr intake, with 0.25 mg/kg AMPH and 1.0 mg/kg FEN decreasing intake to 50% of baseline. The dose-response functions for AMPH and FEN were parallel, with AMPH being approximately four times as potent as FEN.

The top panel of Fig. 2 compares latency to the first meal following AMPH and FEN. Under baseline conditions, the latency to the first meal of each session was about 30 min. Latency to the first meal includes the time between the onset of the session and the first response in the initial procurement component as well as the time to complete the response requirement during the procurement component. The different procurement ratio requirements among baboons influ-

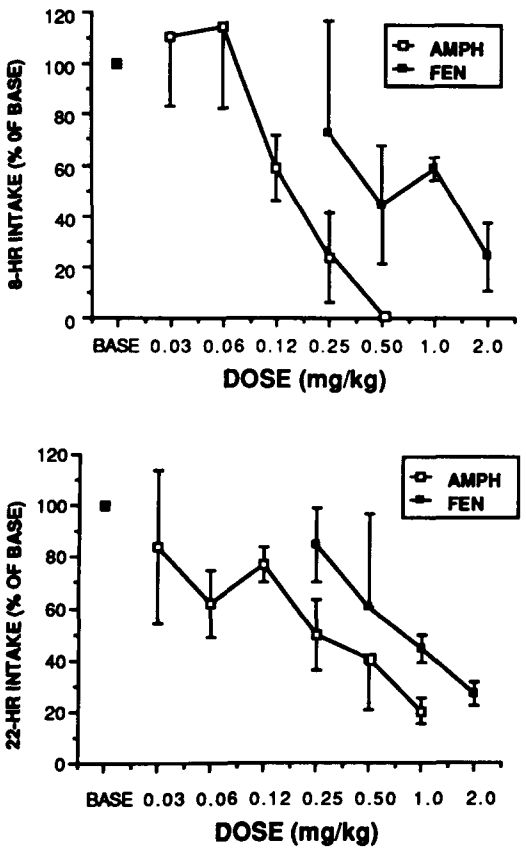

FIG. 1. Mean eight-hr (top panel) and 22-hr pellet intake (bottom panel), expressed as percent of baseline, as a function of dose of AMPH and FEN. Error bars indicate SEMS.

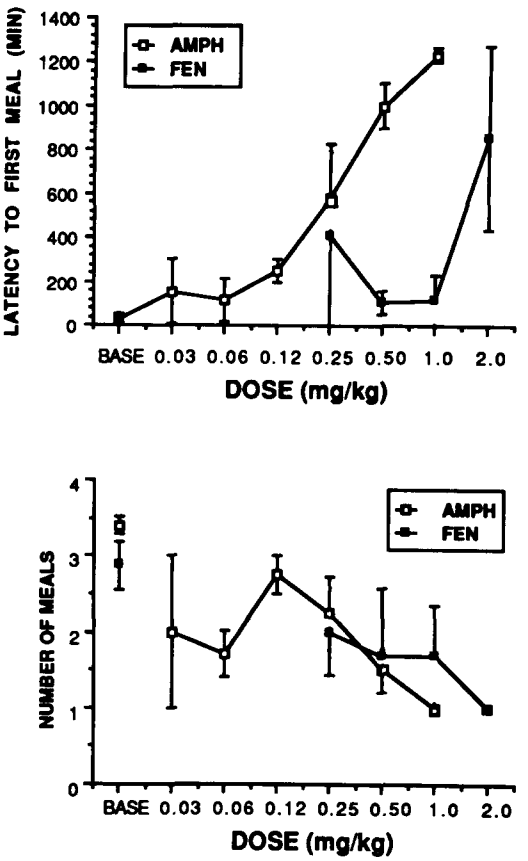

FIG. 2. *Top panel.* Mean latency to the first meal, i.e., consumption component, as a function of dose of AMPH and FEN. *Bottom panel.* Mean number of meals as a function of dose of AMPH and FEN. Error bars indicate SEMS.

ence latency, but this effect is small under baseline conditions. This can be seen clearly in Fig. 2 as the standard error of the mean of the baseline latency is covered by the symbol representing the baseline mean. AMPH produced dose-dependent increases in the latency to the first meal, $t(21)=7.68$, $p<0.001$. In contrast, FEN had no significant effect on latency to the first meal. The large variance following the lowest and highest FEN doses was due to a single baboon having a latency much longer than the remaining animals. The dose (0.25 mg/kg) of AMPH that decreased total intake by 50% increased latency by nine and half hours, while the dose (1.0 mg/kg) of FEN that similarly decreased total intake increased latency by only two hours.

The bottom panel of Fig. 2 compares the total number of meals following AMPH and FEN. Under baseline conditions, the baboons consumed an average of three to three and half meals each day. Both AMPH, $t(21)=-3.28$, $p<0.004$, and FEN $t(16)=-2.02$, $p<0.027$, decreased the total daily number of meals. Meal number decreased to 2.25 following the dose (0.25 mg/kg) of AMPH that decreased total intake by 50%, while the dose (1.0 mg/kg) of FEN that similarly decreased total intake by 50% decreased meal number even further, to 1.67 meals per session.

The mean response rate during the first procurement component prior to the first meal was 0.46±0.05 responses/sec prior to testing AMPH, and 0.55±0.20 responses/sec prior to testing FEN. Neither drug had any significant effect on rate of responding during the first procurement component. Thus, changes in latency described above are not due to decreases in procurement component response rate. The proportion of responses in each IRT-bin during the first procurement component were not distributed evenly [AMPH, $F(5,105)=136.73$, $p<0.001$; FEN, $F(5,80)=142.26$, $p<0.001$]. Approximately 80% of the responses were separated by less than one sec (bin-1), and 10% of the responses were separated by greater than five sec (bin-6). Neither AMPH nor FEN had a significant effect on the distribution of responses during the first procurement component.

Figure 3 compares the effects of AMPH and FEN on eating behavior during the first meal of the session for those baboons who had at least one meal at each dose of drug. All data points represent the mean of at least three baboons with the exception of 1.0 mg/kg AMPH which represents the data of two baboons. The remaining baboons did not eat at all following this dose of AMPH. AMPH significantly, $t(21)=-2.13$, $p<0.045$, decreased the size of the first meal from a baseline value of 134 pellets, and FEN significantly, $t(16)=-2.47$, $p<0.025$, decreased the size of the first meal from a baseline value of 171 pellets (top panel). The dose (0.25 mg/kg) of AMPH that decreased total daily intake by 50%, decreased the size of the first meal to 57% of baseline, while the dose (1.0 mg/kg) of FEN that decreased total daily intake by 50%, only decreased the size of the first meal to 85% of baseline. The duration of the first meal (middle panel)

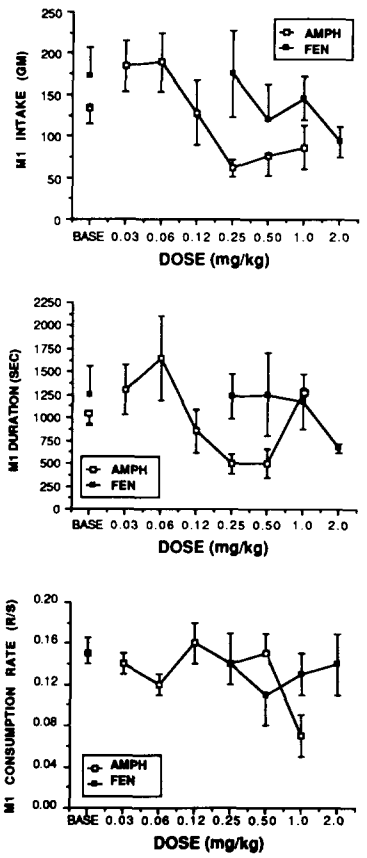

FIG. 3. *Top panel.* Mean weight of pellets consumed during the first meal as a function of dose of AMPH and FEN. *Middle panel.* Mean duration of the first meal as a function of dose of AMPH and FEN. *Bottom panel.* Mean consumption rate (responses/sec), i.e., response rate, during the first meal as a function of dose of AMPH and FEN. Error bars indicate SEMs.

was approximately 18 minutes under baseline conditions. Although AMPH had not statistically significant effect on meal duration, the 0.25 mg/kg dose reduced meal duration to 47% of baseline. In contrast, FEN significantly, $t(16)=-2.25$, $p<0.039$, reduced the duration of the first meal, but this effect was clearly limited to the 2.0 mg/kg dose, as 1.0 mg/kg only reduced meal duration to 94% of baseline. Rate of responding during the first meal (bottom panel) under baseline conditions was 0.15 responses/sec. Neither AMPH or FEN significantly reduced the rate of responding during the first meal of the session.

Figure 4 compares the IRT-distributions of responses as a function of quarter of the meal following AMPH administration. There was a significant effect of IRT-bin, $F(5,105)=55.71$, $p<0.001$, with the greatest proportion of responses separated by less than two sec (bin-1), and the next greatest proportion of responses separated by more than ten seconds (bin-6). In addition, there was a significant quarter of the meal by bin by dose interaction, $F(15,315)=1.87$, $p<0.025$. As the dose of AMPH increased, the proportion of responses separated by less than two sec decreased, but this decrease was not consistent for all quarters of the meal. Following 0.25 mg/kg AMPH (lower left panel), the proportion of responses separated by less than two sec decreased during the second quarter, while following 0.50 mg/kg AMPH (lower right panel), the proportion of responses separated by less than two sec decreased during all quarters of the meal.

Figure 5 compares the IRT-distributions of responses as a function of quarter of the meal following FEN administration. There was a significant effect of IRT-bin, $F(5,80)=29.95$, $p<0.001$, with the greatest proportion of responses separated by less than two sec, and the next greatest proportion of responses separated by more than ten seconds. In addition, there was a significant quarter of the meal by dose interaction, $F(3,48)=6.04$, $p<0.001$. Under baseline conditions (panel A), 50–60% of responses during each quarter of the meal were separated by less than two sec. Administration of FEN decreased the proportion of responses separated by less than two sec to a greater extent as the meal progressed. For example, following 0.50 mg/kg FEN (panel C) the proportion of responses separated by less than two sec decreased as a function of quarter of the meal from 55% to 39%, while under baseline conditions a similar decrease in proportion as a function of quarter of the meal was not evident.

Only small changes in body weight occurred over the course of the experiment: V-3's body weight remained at 36.1 kg, R-82 gained 0.8 kg from a starting weight of 27.8 kg, Z-26 gained 0.4 kg from a starting weight of 36.4 kg, and A-33's body weight remained at 25.0 kg.

DISCUSSION

The results demonstrate clearly that oral AMPH and FEN produce dose-dependent decreases in food intake in free-feeding baboons. The dose-response functions for the two drugs were parallel, with FEN one-fourth as potent as AMPH. The doses that decreased food intake by 50% were smaller than previously reported for reducing food intake in rhesus monkeys given one- to two-hr daily access to food (14,26). This difference in potency supports the previous data indicating that decreasing food deprivation shifts the dose-response function for AMPH to the left (6, 7, 23). The total daily dose of self-administered IV AMPH and FEN that decreased intake to 50% of baseline in baboons was about eight times larger than that used here (16). Differences in route of administration and unit dose make it impossible to compare absolute dosage between these two studies. However, the same relative potency (one to four) of AMPH to FEN was reported in that earlier study (16).

In the current procedure, completion of the response requirement of the procurement component provided access to the consumption component. This allowed the specificity of a drug effect to be assessed by comparing responding between procurement and consumption components. If a drug had no effect on feeding per se, but disrupted food intake due to nonspecific motor deficits, the rate of responding and the pattern of responding in both the procurement and consumption components would be disrupted. If a drug specifically changed the pattern of responding in the consumption component, but not the procurement component, it could be argued that the change in pattern was a specific consequence of an interaction between food intake and drug. An additional advantage of this procedure was based upon the use of non-deprived animals. Nondeprived baboons with relatively continuous access to food should have been sensitive to drug effects on meal initiation (8).

The procedures used in the present paper engendered per-

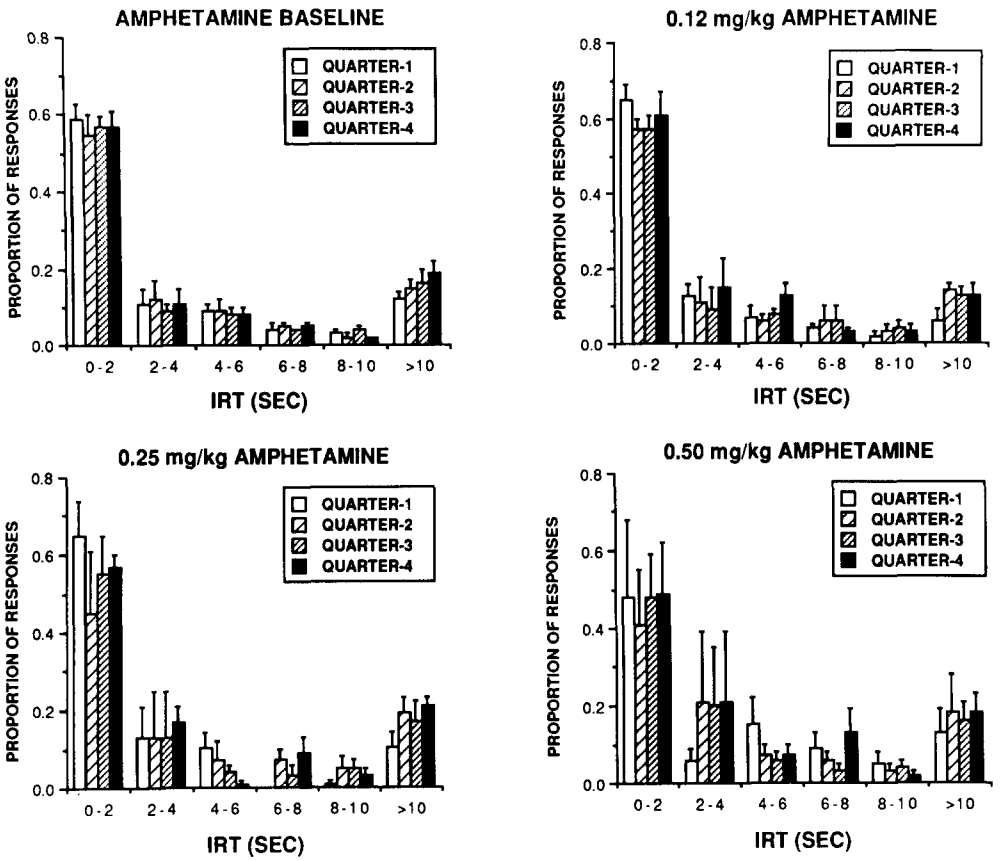

FIG. 4. Mean proportion of responses occurring in each IRT-bin during each quarter of the first meal as a function of AMPH administration. *Upper left panel.* AMPH baseline. *Upper right panel.* 0.12 mg/kg AMPH. *Lower left panel.* 0.25 mg/kg AMPH. *Lower right panel.* 0.50 mg/kg AMPH. Error bars indicate SEMS.

formance during procurement and consumption components that were differentially affected by drugs, and the selective effects of AMPH were different from those of FEN. The most notable difference in the effects of AMPH and FEN was the dose-dependent increase in latency to the first meal following AMPH administration. FEN produced a nonsignificant increase in latency to the first meal, and this effect was only evident following the highest dose. The majority of previous research used rats has reported similar differential effects of these two drugs on initiation of feeding (2, 9, 20, 24), but see (17) for an exception. Research with human volunteers has demonstrated either short, e.g., 30 sec, increases in latency following AMPH (22) or similar increases in latency following both AMPH and FEN (18). If increases in latency following AMPH were due to nonspecific motor effects rather than a specific effect on meal initiation it would be predicted that the pattern and rate of responding during both the first procurement and consumption components would be altered. This was not the case. Once responding started during the procurement component, there was no disruption of either rate or patterning as a function of either AMPH or FEN administration. An alternative explanation about the cause of the differences between drugs with respect to changes in latency may be that FEN has a longer onset of action than AMPH. This is unlikely, however, as two previous studies (14,26) have reported significant dose-dependent decreases in food intake following oral FEN and AMPH given 60 min prior to experimental sessions lasting one to two hours.

Both AMPH and FEN produced dose-dependent decreases in meal frequency. These findings fail to replicate the reports of several laboratories. Blundell and co-workers (2,4) reported that only AMPH decreased the number of meals, while Leibowitz and her colleagues (21,24), reported that neither AMPH nor Nor-FEN had an effect on meal number in free-feeding rats. However, the results do replicate one earlier report (17). In that study, both AMPH and FEN reduced the number of meals in free-feeding lean and obese Zucker rats (17).

AMPH produced dose-dependent decreases in the size and duration of the first meal, while only the highest dose of FEN reduced the size and duration of the first meal. Neither drug had any effect on the rate of responding during the first meal. Unfortunately, many of the baboons had only one meal following a number of the drug doses, making it impossible to analyze the effects of these drugs on intake of the second meal in a consistent way. Previously, FEN has been reported to reduce meal size and rate of eating (4, 5, 9, 17, 24), while AMPH has been reported to decrease meal size and increase rate of eating in rats (4,20).

Analysis of the distribution of IRTs within the first meal

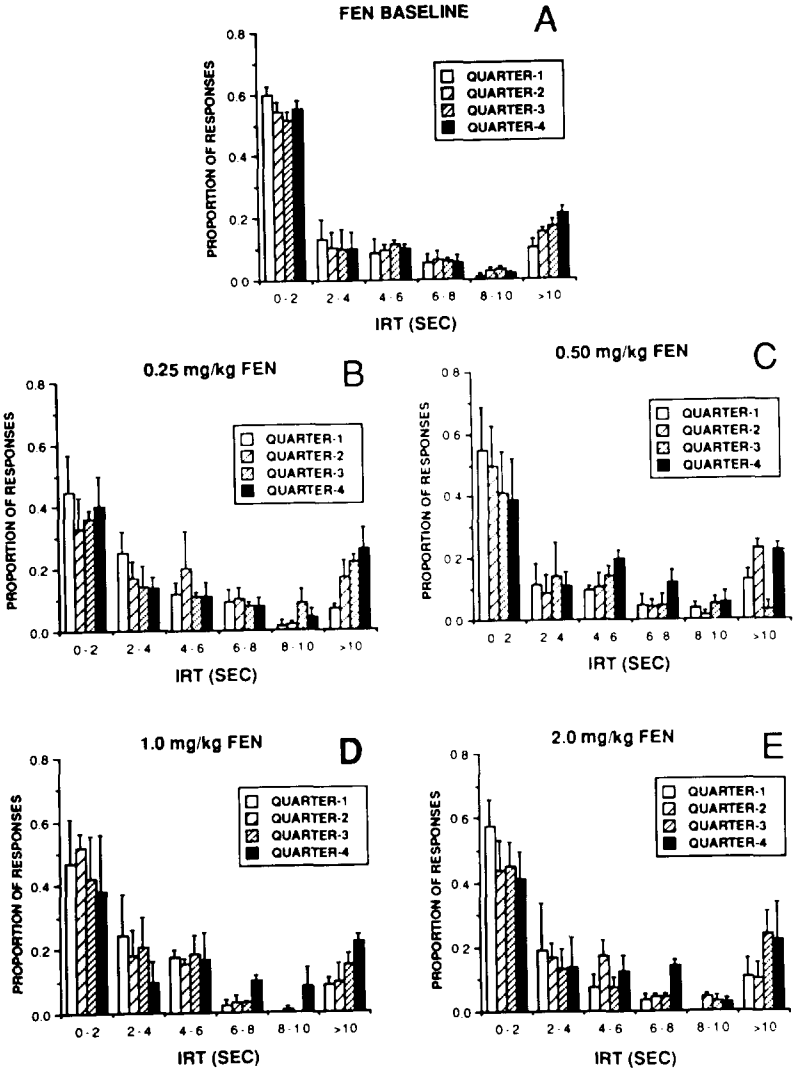

FIG. 5. Mean proportion of responses occurring in each IRT-bin during each quarter of the first meal as a function of FEN administration. *Panel A.* FEN baseline. *Panel B.* 0.25 mg/kg FEN. *Panel C.* 0.50 mg/kg FEN. *Panel D.* 1.0 mg/kg FEN. *Panel E.* 2.0 mg/kg FEN. Error bars indicate SEMs.

indicates that AMPH and FEN had different effects on the pattern of eating. Under baseline conditions, as the meal proceeded, the proportion of responses separated by less than two sec decreased and the proportion of responses separated by more than 10 sec increased. Although significant, this decrease in eating rate as the meal progressed was not as substantial as has been observed with rats (5). The orderly pattern of changes in the IRT-distribution as the meal progressed was disorganized by AMPH. In contrast, the significant quarter by bin interaction following FEN administration suggests that the effect of FEN in decreasing the local rate of eating is specific to the later quarters of the meal. Similar quarter-of-the-meal-dependent shifts in the IRT-distribution as a function of FEN dose were reported in rats (5), but not in humans (22) where FEN decreased rate of eating throughout the meal.

The discrepancy between the effects of AMPH and FEN on the patterning of food intake in the present study and in previous studies may be due to differences in dose, route of administration, species, duration of feeding session, and the response requirement for food. Although the combination of these factors limits direct comparisons among studies, there are consistent differences between AMPH and FEN within studies. Under the current experimental conditions, AMPH reduced intake by increasing latency to the first meal, decreasing first meal size and the number of meals during the session. Low doses of FEN reduced intake by decreasing the size of the first meal and number of subsequent meals. When baboons maintained under the same conditions as in the present experiment were given concurrent access to pellets and a dextrose solution (0.25–0.50 kcal/ml), the same patterns of changes in pellet intake were observed as in the present experiment following AMPH administration, i.e, the latency to the first meal increased, size of the first meal decreased, and the number of meals decreased (13). This similarity between AMPH and the availability of an alternate

source of calories is further evidence that AMPH, in the dose range used here, has a specific effect on food intake.

Although both drugs reduced the number of meals, they had different effects on the temporal distribution of meals. AMPH increased the latency to the first meal, while FEN had little effect on the timing of the first meal, but decreased the number of later meals. These results support the hypothesis that AMPH and FEN affect feeding through different mechanisms [e.g, (1, 2, 20)]. AMPH immediately affected the pattern of intake by increasing latency, while FEN, at least at lower doses, had minimal effect on food intake until feeding actually began. In rats, this effect of FEN was evident within a single meal (2,21), while in this experiment, this effect was evident only after the first meal. These results suggest that the anorectic effect of FEN, but not AMPH, are enhanced by food availability. Foltin and Schuster (14) determined the effects of anorectic drugs on food intake of rhesus monkeys alone, and in combination with intragastric caloric preloading. Intragastric preloading produced greater shifts to the left, i.e., larger effects at smaller doses, of the FEN dose-response function than for dose-response functions of drugs that affect dopaminergic neurotransmission, e.g., phendimetrazine, cathinone, AMPH (14).

The results of the present study also support the hypothesis that AMPH affects food intake by increasing latency to the first meal (4,21). The corollary hypothesis that FEN affects food intake by decreasing meal size, but not meal frequency (1, 20, 24) was not supported by these data. At lower doses, FEN had no effect on the size of the first meal, but decreased the number of subsequent meals suggesting that the previous hypotheses relating changes in single meal intake to FEN may have to be expanded to account for the effects of FEN on the number of meals occurring late in the session. It is clear that although there are differences among species and experimental conditions, drugs that affect dopaminergic function and drugs that affect serotonergic function influence feeding behavior in different ways.

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