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Effects of Food Deprivation on Subjective Responses to *d*-Amphetamine in Humans

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ZACNY, J. P. AND H. DE WIT. *Effects of food deprivation on subjective responses to* d-*amphetamine in humans*. PHARMACOL BIOCHEM BEHAV **34**(4) 791–795, 1989.—The effects of 24 hours of food deprivation on the subjective response to 10 mg oral *d*-amphetamine were studied in 12 healthy normal volunteers. A within-subjects design was used in which subjects ingested amphetamine and placebo capsules in both a fed and a fasting state. Each of the four experimental conditions—FED/DRUG, FED/PLACEBO, FAST/DRUG, FAST/PLACEBO—was enacted twice according to a randomized block design. Three subjective effects questionnaires, the Profile of Mood States, the Addiction Research Center Inventory, and the Visual Analogue Scale, were completed prior to and 1, 3 and 6 hr after the early morning capsule ingestion. Typical elevations in such subjective effects as elation and vigor were obtained after amphetamine ingestion in both feeding conditions, but fasting neither potentiated nor attenuated the drug response. Subjects at the end of the session, however, were more likely in the FAST/DRUG condition than in the FED/DRUG condition to label the capsule they had ingested at the beginning of the session as a stimulant.

Food deprivation Fasting *d*-Amphetamine Subjective effects Ketone bodies Blood glucose Human

IN both rhesus monkeys and rats, food deprivation increases the rate of drug self-administration and the quantity consumed of a number of drugs that are abused by humans (8). The effect occurs across several pharmacologic classes of drugs, including stimulants such as amphetamine and cocaine (19), sedatives (25) and opiates (4), and across different routes of administration (4). The mechanism by which drug self-administration is increased by food deprivation is not known. One explanation is that the reinforcing effects of a drug are increased by food deprivation (8,15). The reinforcing efficacy of a drug may be enhanced through an interaction between the drug and altered brain neurotransmitter function during fasting (e.g., alterations in dopamine or serotonin) (2, 17, 19, 24). Alternatively, the reinforcing efficacy of a drug may be influenced by interactions among different reinforcers concurrently available in the environment. For example, if one reinforcer (e.g., food) is removed from an organism's environment, then the reinforcing efficacy of the remaining reinforcers (e.g., drug) in that environment may be enhanced.

Other properties of a drug besides its reinforcing effects may be affected by food deprivation. Several studies with laboratory animals have examined the effects of food deprivation on behavioral and physiological responses to amphetamine. The results of these studies have been complex. For example, food deprivation potentiates the increased locomotor activity observed after amphetamine (1, 13, 14, 27), but attenuates the hypothermic effect of amphetamine (26). Complex interactions have also been observed between food deprivation and amphetamine's effects on brain neurotransmitters and their precursors (e.g., tryptophan, striatal dopamine levels) (20).

Several studies have also explored whether the discriminative stimulus (DS) effects of drugs are altered by food deprivation. In one study using food-rewarded behavior (18), food deprivation increased sensitivity to morphine in rats, i.e., the dose-response function for the morphine discriminative stimulus (DS) was shifted to the left. However, these results were not replicated by another investigator who used shock-avoidance (31). Further, in another study using food-rewarded behavior (29), the DS properties of phencyclidine were not affected by food deprivation.

Little is known about the effects of food deprivation, or fasting, on either the reinforcing or the subjective effects of drugs in humans. The present study was designed to assess the effects of an acute fasting period (24 hours) on the subjective effects of 10 mg oral *d*-amphetamine in normal volunteers. This moderate dose of amphetamine reliably produces a characteristic profile of elevated mood in normal volunteers.

METHOD

Subjects

Six males and six females (age range: 21–34, mean age: 26

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years) participated in the study. They were recruited from the local university community via newspaper or bulletin board advertisements. Individuals who normally consumed less than two meals a day or who did not eat breakfast on a regular basis were not accepted because it was thought that the deprivation condition would have little impact on these individuals. Prior to participation, subjects underwent a physical examination and psychiatric interview. Volunteers with histories of drug abuse or dependence, or significant psychiatric or other medical disorders were not accepted. Informed consent was obtained. In the consent form, the study was outlined and side-effects of any drug subjects might be given were indicated. Subjects were told that the drugs might come from one of five classes—anorectic, sedative/tranquilizer, alcohol, antihistamine or placebo—and the doses of prescription drugs would be within the daily therapeutic range. Subjects were paid for study participation during a final debriefing session.

General Procedure

The experiment consisted of eight sessions, during which subjects ingested either placebo or *d*-amphetamine (10 mg) capsules in either a fed or fasting state. These four conditions—FED/DRUG, FED/PLACEBO, FAST/DRUG, FAST/PLACEBO—were enacted twice according to a randomized block design. [One subject (AK) participated in only one replication of each condition.]

Feeding manipulation. In the FAST condition, subjects were instructed to start the fast between 9 and 10 a.m. on the day before the experimental session. Subjects were told not to eat any solid food or drink any beverage containing more than 10 calories from this time until six hours following the capsule ingestion on the following day. When they were in the FED condition, subjects were told to eat normally on the day prior to the session and to consume a light snack (provided by the experimenter) prior to their bedtime that evening. In both the FED and FAST conditions, subjects were instructed not to eat prior to reporting to the laboratory on the day of the session to minimize differences in stomach load in the two feeding conditions. Rate of drug absorption can be increased or decreased by food in the GI tract (30), thus potentially altering magnitude of drug effects. We did not want differential rates of drug absorption to be a confounding variable in our study because the food deprivation effect is not thought to be due to this pharmacokinetic variable (8). However, in the FED condition, subjects were provided with a 150-calorie lemonade-flavored fructose drink at 7 a.m. the morning of the session, whereas in the FAST condition, they consumed a drink of the same volume that was sweetened with a low-calorie sugar substitute and contained only 10 calories. Subjects were not told the caloric value of the drinks. Six times during the 24 hr prior to the session, subjects rated their hunger on a 100-mm line.

Experimental sessions. Subjects arrived at the laboratory between 9 and 10 a.m. on the day of the session (Tuesdays and Fridays). After giving urine and blood samples, subjects filled out three mood questionnaires, the Profile of Mood States (POMS), the Addiction Research Center Inventory (ARCI), and the Visual Analogue Scale (VAS) (see below), and then ingested a capsule. Both the subject and the experimenter were blind as to the contents of the capsule. After ingesting the capsule, the subjects were free to leave. They took three additional sets of mood forms with them with instructions to fill them out 1, 3 and 6 hours later. In addition, they took four drinks with them and were to consume these drinks 2, 3, 4 and 5 hours after capsule ingestion. Each drink contained 10 calories in the FAST condition and 75 calories in the FED condition. Between the hours of 3 and 4 p.m., subjects returned to the laboratory to give urine and blood samples, fill out an End-of-Session questionnaire (see below), and receive instructions as to whether they were to fast or not prior to the next session.

Subjective effects questionnaires. The POMS consists of 72 adjectives commonly used to describe momentary mood states. Subjects indicate how they feel at the moment in relation to each of the 72 adjectives on a 5-point scale ranging from 'not at all' (0) to 'extremely' (4). There are eight clusters of items (scales) which have been separated using factor analysis (Anxiety, Depression, Anger, Vigor, Fatigue, Confusion, Friendliness, and Elation). The value of each scale is determined by adding the numbers checked for each adjective in the cluster and dividing the total by the number of adjectives. Two additional scales, Arousal and Positive Mood, were derived from the other scales as follows: Arousal = (Anxiety + Vigor) − (Fatigue + Confusion); Positive Mood = Elation − Depression.

The Addiction Research Center Inventory (ARCI) is a true-false questionnaire with empirically derived scales that are sensitive to the effects of a variety of classes of abused drugs (21). A short form of the inventory was used, consisting of five scales with a total of 49 items (28). The five scales were the Morphine-Benzedrine Group (MBG), a general measure of drug-induced euphoria, the Benzedrine Group (BG), an amphetamine scale consisting mainly of items relating to intellectual efficiency and energy, the A, a measure specific for dose-related effects of *d*-amphetamine, the LSD, a measure of dysphoria and somatic symptoms, and the Pentobarbital-Chlorpromazine-Alcohol Group (PCAG), a measure of sedation. The Visual Analogue Scale (VAS) is a form that has six horizontal 100-mm lines, each labelled with an adjective ('stimulated,' 'high,' 'anxious,' 'sedated,' 'down' and 'hungry'). Subjects were instructed to place a mark on each line indicating how they felt at the moment, from 'NOT AT ALL' to 'EXTREMELY.'

On the End-of-Session Questionnaire, subjects were first asked to identify whether or not they had received an active drug that session. If subjects guessed they had received an active drug, they were asked to classify the drug effects as either primarily sedative-like or stimulant-like. Subjects were also asked to rate on a 100-mm line their liking for the capsule, and their activity level during the 6-hr postdrug ingestion period. Lastly, subjects were asked whether they had experienced any unusual reactions.

Blood and urine sampling. A drop of blood was obtained from one of the fingers of the subject, placed on a glucose reagent strip (Glucostix, Ames Inc.), and analyzed by a blood glucose-metering device (Glucometer, Ames Inc.). A ketone body reagent strip (Ketostix, Ames Inc.) was placed in the urine sample for determination of ketosis. These measures served two purposes: as 'incentives' for the subjects to comply with our instructions and as indicators of the physiological consequences of the 24-hour fast. Subjects were told at the beginning of the study that the blood and urine samples would be used to determine whether or not they were complying with the fasting instructions. While in actuality these measures do not reliably indicate whether an individual subject has been fasting, they might provide some verification of compliance in the entire group. In a pilot study in which subjects resided on a clinical research ward where food availability was strictly controlled, it was determined that 24 hours of food deprivation was often, but not always, associated with lowered blood glucose levels and/or ketosis.

Data analysis. Subjective effects data from the POMS, ARCI and VAS and the blood glucose levels were analyzed with univariate analysis of variance for repeated measures (16). Three-way ANOVA was used (Feeding Condition × Drug × Hour). Liking and activity-level scores from the End-of-Session questionnaire were analyzed by two-way ANOVAs (Feeding Condition × Drug). Hunger ratings taken prior to experimental sessions were analyzed by two-way ANOVA (Feeding Condition × Hour). F-values were considered significant for $p<0.05$, with adjust-

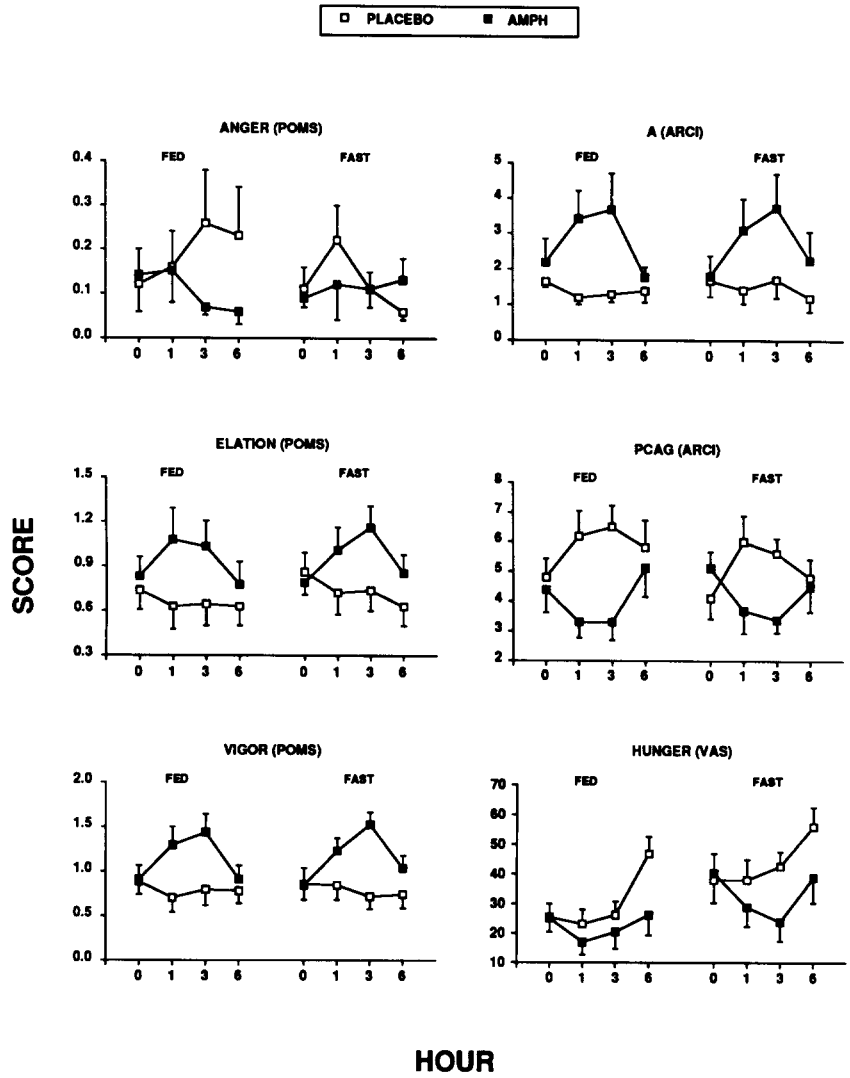

FIG. 1. The effects of 10 mg *d*-amphetamine (solid squares) and placebo (open squares) as a function of feeding condition (FED: left side of graph, FAST: right side of graph) prior to and 1, 3 and 6 hr after capsule ingestion on scores from the ANGER (top left frame), ELATION (middle left frame), and VIGOR (bottom left frame) scales of the POMS, the A (top right frame) and PCAG (middle right frame) scales of the ARCI, and the HUNGER (bottom right frame) scale of the VAS. Each point is the mean (±SEM) across 12 subjects.

ments of within-factors degrees of freedom (Huynh-Feldt) to protect against violations of symmetry (16).

RESULTS

Subjective Effects

There were several Drug or Drug × Hour effects, indicating that 10 mg amphetamine produced a spectrum of subjective effects, but there was little evidence that fasting altered the subjective effects of amphetamine. Significant Drug or Drug × Hour effects were obtained on the Vigor, Elation, Friendliness, Arousal and Positive Mood scales of the POMS, the PCAG, BG, MBG, and A scales of the ARCI, and the Stimulated, High and Hungry ratings of the VAS. Figure 1 shows six scales from the three subjective effects questionnaires. It is clear that fasting did not consistently attenuate or potentiate the subjective effects of amphetamine. The only Feeding Condition × Drug × Hour interaction obtained in the three subjective effects questionnaire was on the Anger scale of the POMS (top left frame of Fig. 1), $F(3,33)=4.0$, $p<0.05$. Additional ANOVAs conducted on the three questionnaires including the two replications, i.e., Sessions, as a factor (i.e., Feeding Condition × Drug × Session × Hour), revealed that the subjective effects of amphetamine in the fasting condition did not differ across sessions. Not surprisingly, hunger ratings from the VAS were affected by Feeding Condition, $F(1,11)=12.8$, $p<0.005$, with generally higher hunger ratings in the FAST conditions than in the FED conditions.

Drug-liking scores were not affected by Feeding Condition. However, drug-liking ratings were significantly higher after DRUG sessions than after PLACEBO sessions, $F(1,11)=32.7$, $p<0.001$. Average liking scores (0–100 scale) from DRUG and PLACEBO sessions were 59.9 (3.3) and 39.1 (2.1), respectively (SEM in parentheses). Activity rating scores were also unaffected by Feeding Condition. However, ratings of overall activity were

TABLE 1
DRUG LABELLING*

	Experimental Conditions			
	Placebo		Amphetamine	
Drug Label	FED	FAST	FED	FAST
Placebo	48	59	30	13
Stimulant	4	18	57	74
Sedative	48	23	13	13

*Each value is the percentage of instances that either placebo or amphetamine was labelled as having placebo, stimulant-like, or sedative-like effects in both the FED and FAST conditions. Each subject (except subject AK) was tested twice under each of the experimental conditions. Each value is derived from 22–23 drug labels.

significantly higher after DRUG sessions than after PLACEBO sessions, $F(1,11)=18.2$, $p<0.001$. Average activity scores (0–100 scale) from DRUG and PLACEBO sessions were 64.8 (4.1) and 50.3 (4.3), respectively.

Ratings of hunger were obtained at different time points during the 24 hours prior to experimental sessions in both the FED and FAST conditions. There was a significant Feeding Condition × Time interaction, $F(6,60)=13.1$, $p<0.001$, with hunger ratings tending to increase across time in the FAST condition.

Drug Identification

Table 1 shows the percentage of occasions that amphetamine and placebo were identified as having placebo-, sedative- or stimulant-like effects. Subjects were slightly less accurate identifying placebo capsules in the fed state than in the fasting state (48% vs. 59% accuracy, respectively). Chi-square analyses were performed to determine if the percentage of instances placebo was correctly labelled in the FED and FAST conditions differed significantly from chance (i.e., 50%) levels. In neither feeding condition did accuracy levels differ from chance. However, subjects were more accurate identifying amphetamine as having stimulant-like effects when they were in the fasting state than when they were in the fed state (74% vs. 57% accuracy, respectively). Chi-square analyses revealed that subjects in the FAST condition labeled the drug as having stimulant-like effects more often than chance ($\chi^2=23.0$, $p<0.05$), whereas in the FED condition, correct amphetamine labelling was at chance level.

Physiological Measures

Seventeen of the 45 urine samples obtained at Hour 0 (38%) and 18 of the 46 samples obtained at Hour 6 (39%) in the FAST sessions tested positive for ketone bodies. Only one of the 46 urine samples obtained at Hour 0 and two of the 46 samples obtained at Hour 6 in the FED sessions tested positive for ketone bodies. Mean blood glucose levels did not differ as a function of Feeding Condition, Drug Condition or Hour. Mean blood glucose levels collapsed across Drug Condition and Hour were 78.6 (2.5) and 81.3 (2.9) in the FAST and FED sessions, respectively (SEM in parentheses).

DISCUSSION

In the present study, the subjective effects of 10 mg amphetamine were very similar in the FED and FAST conditions. A spectrum of typical amphetamine-like subject effects, including increases in vigor and euphoria and a decrease in sedation, were noted in both feeding conditions. Subjects were more likely in the fasting state than in the fed state to accurately identify amphetamine at the end of the 6-hr session, but this increased labelling accuracy was not accompanied by corresponding differences in subjective effects across feeding conditions. It is unclear, then, what effects of amphetamine were used in the drug identification process.

Although blood glucose levels were not significantly lower in the FAST condition than in the FED condition, and urinary ketone bodies were present in only about 40% of the samples obtained in the FAST condition, these values were comparable to results obtained in an earlier inpatient fasting study, in which compliance to a 24-hr fast was strictly monitored. While it is possible that subjects failed to comply with the fasting instructions, the physiological data and the fact that subjects in the FAST condition reported greater hunger before and during the session than in the FED condition suggest that noncompliance was not a major factor in the present study.

It is possible that a particular physiological consequence of fasting, e.g., ketosis, is a necessary condition in order for a food deprivation effect to be observed. That is, perhaps only in those subjects whose physiology reflected fasting did food deprivation alter the subjective effects of amphetamine. To investigate this possibility, data from the ARCI were reanalyzed, using only those subjects ($N=7$) who exhibited ketosis in a PLACEBO and DRUG session in the fasting state. In this analysis as well, food deprivation did not alter the subjective effects of amphetamine. This additional analysis provides further evidence that the absence of changes in subjective effects by food deprivation in the present study was not due to subject noncompliance to the fasting regimen, since a food deprivation effect was not detected even in those subjects whose physiological state was altered by fasting.

Several aspects of our experimental procedure may have been responsible for the lack of a food deprivation effect. First, food deprivation may indeed alter the subjective effects of amphetamine, but at lower doses than the one tested in the present study (10 mg). In several animal studies, increases in drug intake as a result of food deprivation was apparent with lower, but not higher concentrations of a drug (9–11). Although 10 mg is not considered to be a high dose, different results might have been obtained had we tested a 5 mg dose, a dose which still reliably produces subjective effects (12,22).

It is possible that different results might have been obtained if subjects in the FED condition had been relatively more sated during the session. Subjects fasted overnight prior to the session, and although they were given fructose drinks before and during the daytime session, they were probably ingesting fewer calories than they would normally ingest via a solid food breakfast and lunch. Indeed, their hunger ratings suggest they were moderately hungry in the FED condition (see Fig. 1). The possibility exists, then, that subjects were food-deprived in both feeding conditions, and that the difference in the degree of food deprivation across feeding conditions was not large enough to produce any differences in subjective effects of amphetamine across conditions. Related to this, different results might also have been obtained if subjects in the FAST condition had been food-deprived for a longer period of time than 24 hr prior to the sessions. The fact that acute food deprivation (i.e., 24 hr) did not impact on subjective effects of amphetamine is not necessarily discordant with results from animal food deprivation studies. An acute period of food deprivation also does not potentiate the reinforcing efficacy of orally administered drugs in animals (8). Only after a period of chronic food deprivation during which the animal is responding for drug does drug intake increase, relative to food satiation levels (7). However, it must be acknowledged that it would be very difficult to recruit subjects for such studies in which one of the requisites

would be frequent or very long periods of fasting.

Finally, it is possible that the use of sweetened drinks in the FAST condition obscured a possible food deprivation effect. In laboratory animals, sweet substances, whether caloric or noncaloric (e.g., glucose, sucrose, saccharin), reduce drug intake (3, 6, 23). Thus, the presence of sweetened drinks in the FAST condition may have reduced the contrast between the FAST and the FED conditions, thus masking a possible difference.

In conclusion, 24 hr of food deprivation had no effect on the subjective effects of 10 mg of oral *d*-amphetamine. Subjects were, however, more accurate in identifying amphetamine as a stimulant in the fasting state. It may still be feasible to examine the impact of acute (i.e., 24 hr) food deprivation on subjective effects of drugs in humans if a route of administration other than the oral route is used. In animal studies, food deprivation increases rates of self-administration much more rapidly when the drug is administered intravenously than when the same drug is administered orally (5). It is conceivable, therefore, that an acute period of food deprivation may alter the subjective effects of a drug if that drug is administered intravenously, when absorption rate and onset of drug effects is more rapid.

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