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Cannabinoids and Appetite Stimulation

RICHARD D. MATTES,*[1] KARL ENGELMAN,† LESLIE M. SHAW† AND MAHMOUD A. ELSOHLY‡

*Monell Chemical Senses Center, 3500 Market St., Philadelphia, PA, 19104
†Hospital of The University of Pennsylvania, Philadelphia, PA, 19104
‡University of Mississippi and ElSohly Laboratories, Inc., Oxford, MS 38655

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MATTES, R. D., K. ENGELMAN, L. M. SHAW AND M. A. ELSOHLY. *Cannabinoids and appetite stimulation.* PHARMACOL BIOCHEM BEHAV **49**(1) 187–195, 1994.—Appetite stimulation by cannabinoids is highly variable. Four within-subject design studies explored the effects of age, gender, satiety status, route of drug administration, and dose on intake. One study involved a single oral administration of active drug (15 mg males, 10 mg females) or placebo to an age and gender stratified sample of 57 healthy, adult light marijuana users. Eleven subjects received single doses by oral, sublingual, and inhaled routes in a second study. In the third study, 10 subjects ingested a single oral dose in fasted and fed states. A 2.5 mg dose was administered b.i.d. for 3 days by oral and rectal suppository routes in the fourth study. Mean daily energy intake was significantly elevated following chronic dosing by rectal suppository, but not oral capsule, relative to all acute dosing regimens except inhalation. Total daily energy intake was comparable on fed and fasted days, suggesting satiety mechanisms were not impaired by the drug. Subject age, gender, reported "high," and plasma drug level were not significantly associated with drug effects on food intake.

Marijuana Food intake Satiety Appetite

NUMEROUS therapeutic applications for cannabinoids, components of marijuana, and their analogs are currently being evaluated (5,9,25,29). One such potential use is as an appetite stimulant in patients with cancer or AIDS (31). Anecdotal reports and descriptive studies [e.g., (3,16,19,20,28,36)] indicate that one or more of these compounds stimulates ingestive behavior and enhances the appreciation of food. In one survey (19), 91% of a sample of 131 male and female moderate to heavy marijuana users reported eating every time they smoked the drug. Eighty-five percent claimed to ingest greater quantities of food when under the influence of the drug, with 67% indicating they would continue to eat even when they were no longer hungry. This apparent inhibition of satiety has been noted by others (4,15,16). An appetite-stimulating property has also been noted in several controlled studies with healthy adults (13,21,24) and in clinical investigations (10,32,34,37), although not invariably (6).

Therapeutic exploitation of the appetite stimulating properties of these compounds will require a better understanding of the optimal conditions for their use. Several potentially problematic issues have been identified in the literature. First, the effect may be dependent upon social facilitation and environmental familiarity. This was exemplified in a study noting increased intake only among subjects allowed to socialize with other marijuana users after smoking the drug (12). Such conditions may not be available for the majority of patients prescribed this agent.

Second, there is a high incidence of disconcerting side effects (e.g., sedation, dry mouth) associated with delta-9-tetrahydrocannabinol (THC) that is positively related to age (14). Less dramatic increases in appetite have been noted in older individuals [e.g., (37) vs. (10) or (34)] who may represent a substantial proportion of the population in need of an appetite stimulant.

Third, there are reports that absorption of the drug from the GI tract can be highly variable (2,38), and capsules are the only FDA approved therapeutic formulation. Appetite stimulation following acute administration of THC is also highly variable (21). Whether this is related to drug absorption is unknown because plasma drug levels have rarely been monitored in feeding studies.

Fourth, the optimal dose level and frequency for stimula-

[1] To whom requests for reprints should be addressed.

tion of appetite is not established. As long ago as 300 AD it was reported that low doses stimulate intake, whereas higher doses are inhibitory (8). Enhanced intake or improved body weight status has been noted in several (10,31,32,34), although not all (6), studies exploring the antiemetic efficacy of oral THC following doses in the range of 10–15 mg/m^2 body surface area. In addition, the benefit was associated with development of a subjective "high" sensation. However, recent open studies suggest the greatest benefit may be realized at a dose of 2.5 mg b.i.d., where subjective sensations are minimal (31).

Related to the dosing issue are open questions about the best route of drug delivery. Capsules of THC taken orally are well accepted by patients, but the drug is often poorly absorbed (2,26,38), especially in patients experiencing repeated bouts of emesis. Smoking marijuana leads to higher plasma THC levels (the principal psychoactive cannabinoid), more consistent subjective high reports, and more reliable appetite-stimulating effects compared to oral administration (2,39). However, because this form of delivery requires smoking the drug and is not currently legal, it is objectionable to many patients. Intravenous delivery also leads to high plasma drug levels, but is impractical in an ambulatory population. Recently, a rectal suppository formulation has been developed, but its therapeutic efficacy and patient acceptability remain to be established (26).

The present series of studies explored the appetite stimulating effects of THC and provide insights on each of the potential therapeutic limitations noted above. The ability of the drug to stimulate intake independent of social influences was determined by monitoring intake in individuals accompanied only by a research technician for each testing session. Discrepancies in intake associated with subject age were examined using an age and gender stratified sample in one study. The relationship between appetite stimulation and plasma drug and subjective "high" levels were evaluated by collecting this information at regular intervals following acute and chronic dosing. The question of whether the increase in intake is attributable to suppression of satiety was assessed by comparing intake in subjects administered the drug after a fast or large meal. Finally, information on the optimal dose and route of administration was addressed by contrasting results after administration of the drug by oral, sublingual, inhaled, and rectal routes and as a single high dose vs. a lower dose twice daily for 3 days.

METHOD

Study Protocols

Data are presented from four studies, all of which had within-subject designs. The first was a double-blind, placebo-controlled, single oral dose study involving an age and gender stratified study population (acute oral study). In the second, subjects were monitored after single oral, sublingual, and smoked doses (multiroute study). The third involved administration of the THC either PO or PR b.i.d. for 3-day periods (chronic study), and the fourth assessed food intake following single oral dosing of subjects in fasted and fed states (satiety study). Different individuals were enrolled in each study. All subjects were recruited by public advertisements and received monetary compensation for their participation. Subjects were informed that each study's aim was to document the physiological actions of the drug; dietary effects were never mentioned. These studies were approved by the Committee on Studies Involving Human Beings at the University of Pennsylvania.

Acute Oral Study

This study was designed to determine whether ingestion of the currently FDA-approved formulation of THC stimulates energy intake and alters the type, nutrient composition, or taste properties of selected foods.

Subjects. Consecutively presenting subjects were recruited until 12 males and 12 females in the 20–30- and 30–40-year-old age brackets were enrolled. Four males and three females 40–50 years of age and two females between 50 and 60 years of age were also entered (total n = 57). All participants reported current use of marijuana between twice per year and twice per week. Eligibility was also based upon absence of acute or chronic health disorders or use of medications that could influence dietary intake, sensory responsiveness, or salivary function. No subject had a history of psychiatric disorders or adverse reactions to psychoactive drugs or marijuana. All subjects had normal physical exams, hematological and urine tests, EKG, and premenopausal females had negative pregnancy tests and were not lactating. All subjects refrained from illicit drug use for the duration of their participation as determined by urine screening. Patient characteristics are presented in Table 1.

Protocol. Participants reported to the hospital at 0800 h after an overnight fast. Vital signs were checked, blood, urine, and saliva samples were collected, a dietary questionnaire was completed, and a battery of chemosensory tests [described elsewhere (27)] was administered. A standard breakfast (421 kcal) comprised of one buttered (5 g) English muffin (57 g), orange juice (240 ml), and 2% milk (240 ml) was consumed in its entirety. Immediately afterwards, a single dose (15 mg for males, 10 mg for females) of delta-9-THC in sesame oil (Marinol®, Unimed, Inc, Somerville, NJ) or matched placebo was swallowed. At 1000 h a tray of preweighed foods (sandwich cookies, cupcakes, chocolate candies, bananas, red apples, pudding, carrots, fruit punch, potato chips, corn chips, peanuts, cheese, crackers, dill pickles, V-8 juice, plain yogurt, green apple, sour hard candies, grapefruit, cranberry juice, bittersweet chocolate, radishes, walnuts, celery, raw broccoli, orange marmalade, bitter lemon drink) was made available for the duration of the test day. This array of foods provided options that were rated by other subjects in previous studies as primarily sweet, sour, salty, or bitter. Vital signs were taken and the dietary questionnaire was completed at this time and hourly for the duration of the day. Sensory testing and blood draws were repeated at 1100, 1300, and 1500 h. Lunch was self-selected from a menu containing about 60 items plus condiments at 1100 h and the preweighed items were presented at 1200 h. Between scheduled activities, subjects were free to engage in quiet recreational activities on the hospital floor. Only one subject was tested per day. Following subject release (at approximately 1800 h), all foods were reweighed to determine the amounts consumed. A technician remained with the subject at all times to ensure their safety and the reliability of food consumption (i.e., no food was given to other patients or hoarded for later consumption). A minimum of 3 weeks was interposed between sessions to ensure that any drug administered during a study day was cleared before subsequent testing.

Multiroute Study

This study explored the acute appetite stimulating effects of THC following different routes of administration.

TABLE 1
SUBJECT CHARACTERISTICS

	Study			
	Acute Oral	Multiroute	Satiety	Chronic
Male/female	28/29	9/2	4/6	3/3
Age (years)	31.3 ± 1.2	27.3 ± 2.8	25.0 ± 2.8	33.3 ± 3.3
BMI (wt/ht^2)	23.4 ± 0.5	22.7 ± 0.5	22.8 ± 0.9	22.2 ± 0.2
Race (White/African American Hispanic/Oriental)	50/5/1/1	9/2/0/0	8/0/0/2	6/0/0/0
Smoke cigarettes (Y/N)	10/47	3/8	3/7	3/3
Age first used marihuana (years)	17.5 ± 0.6	18.5 ± 0.6	16.5 ± 0.7	18.8 ± 0.8
Mean level of use (times/year)	9	4	8	5
Duration of current use level (years)	4.3 ± 2.0	5.8 ± 0.7	3.1 ± 0.7	5.5 ± 0.5

Subjects. Eleven subjects meeting the eligibility criteria established for the acute oral study were recruited. No attempt was made to stratify the sample for age or gender. Subject characteristics are listed in Table 1.

Protocol. The testing protocol was identical to that used in the acute oral study except multiple routes of drug delivery were tested. After breakfast, a single dose (15 mg for males, 10 mg for females) of delta-9-THC in sesame oil (Marinol®, Unimed, Inc, Somerville, NJ) was swallowed, allowed to dissolve under the tongue or a single 710–795 mg marijuana cigarette (2.57 ± 0.06% delta-9-THC) was smoked (supplied by the National Institute on Drug Abuse, Research Triangle Park, NC). Smoking entailed inhaling for 3 s, holding 12 s, exhaling, waiting 15 s and repeating until the cigarette was burned down to a 2 cm stub. Each test session was separated by at least 3 weeks. Because of concern about lingering drug effects on behavior, subjects remained in the hospital until 2300 h. The snack tray was available until 2000 h. Subjects were provided a self-selected dinner at 1800 h (the nutrient content of which was measured).

Chronic Study

This study was designed to provide preliminary data on the appetite stimulating effects of THC following repeated low (2.5 mg) doses by two (oral and rectal suppository) routes.

Subjects. Three males and three females meeting the eligibility criteria established for the acute oral study were recruited. Subject characteristics are listed in Table 1.

Protocol. The types of measures assessed (e.g., sensory function, blood pressure, salivary function) were identical to those monitored in the acute oral study, but the timing of activities differed. Blood was drawn at 0800, 1200, 1600, 2000, and 2300 h each day. Sensory testing was conducted at 0800 and 1600 h the first day and only at 1600 h on the subsequent two days. Eating opportunities included a self-selected breakfast (0800 h), lunch (1200 h), dinner (1730 h), and a snack tray (1000–2300 h) each day. A 2.5 mg dose of delta-9-THC was administered PO or PR (as the hemisuccinate ester, supplied by ElSohly Laboratories, Oxford, MS) at 0900 and 1700 h. The two 3-day test sessions were separated by a minimum of 3 weeks.

Satiety Study

In this study, the appetitive effects of THC administration to subjects in a fed and fasted state were contrasted to determine whether the drug alters satiety. Failure to compensate dietarily for the energy provided by the pretreatment breakfast would indicate a disruption of satiety mechanisms.

Subjects. Characteristics of the 10 subjects who met the eligibility criteria used in the acute oral study are listed in Table 1.

Protocol. The testing protocol was identical to that used in the acute oral study except subjects either received no morning meal or one containing 455 kcal comprised of scrambled eggs (87.3 g), bacon (14.3 g), half of an English muffin (28 g) with 7.5 g of margarine, orange juice (120 cc), and milk (240 cc of whole milk). Immediately after breakfast, a single dose (15 mg for males, 10 mg for females) of delta-9-THC in sesame oil (Marinol®, Unimed, Inc, Somerville, NJ) was swallowed. The 2 test days were separated by a minimum of 3 weeks.

TEST PROCEDURES

Hematology and Urinalysis

Prior to testing, a single casual urine sample was collected in a polycarbonate container and screened by the EMIT DAU test for cannabinoids (20 ng/ml threshold concentration) (Syva Co., Palo Alto, CA). All screens were negative.

Blood was drawn by venipuncture into 7 cc sterile glass syringes containing EDTA. Collections occurred at baseline 2, 4, and 6 h for the acute oral study. An additional sample was collected 8 h postdosing for all other acute dosing studies and at 0800, 1200, 1600, 2000, and 2300 h in the chronic study. Samples were centrifuged at room temperature, transferred to glass test tubes, and frozen for later analysis. Plasma levels of delta-9-tetrahydrocannabinol and 11-nor-delta-9-THC-9-carboxylic acid were determined via electron-capture negative chemical-ionization mass spectrometry (35). Area under the curve for drug level over time was determined by the trapezoidal procedure (GraphPad, InPlot, San Diego, CA).

Dietary Assessment

Quantities of items consumed were determined covertly by weighing the remaining preweighed foods at the end of each test session. Total daily energy, energy from predominantly sweet, salty, sour and bitter items, energy obtained from different food groups as well as the proportions of energy from carbohydrate, protein, and fat were computed using version 4.0 of the Nutritionist III Nutrient Database (N-Squared Computing, Salem, OR). Questionnaires administered hourly elicited information about appetite and food cravings.

Statistical Analyses

The effects of drug administration on dietary intake were assessed by repeated measures analysis of variance with treatment (active vs. placebo (acute oral study) or oral vs. sublingual vs. smoked (multiroute study) or fed vs. fasted (satiety study) or oral vs. suppository (chronic study) and time (0, 2, 4, 6 h postdosing) as factors. The effect of subject age on treatment responses (i.e., reported "high," plasma drug level, intake) were determined by linear regression and analysis of variance. Associations between intake variables, age, plasma drug levels, and subjective "high" ratings were determined by computing Pearson correlation coefficients. Where multiple tests were planned, a probability level of 1% was used as the criterion for statistical significance; otherwise a value of 5% was applied. Data are presented as means ± standard error of the mean.

RESULTS

Plasma Drug Levels

Figure 1 presents data on plasma levels of THC (top panel) and its carboxy metabolite (bottom panel) over the 8-h period following dosing by oral, inhaled, sublingual, and rectal routes as well as after oral administration following a standard breakfast (oral fed), or an overnight fast (oral fasted). A different blood collection schedule was used in the chronic study where the suppository was administered. Consequently, to permit direct comparisons across routes of administration, the suppository data presented were obtained from two individuals who participated in separate test sessions where this formulation was given acutely and the timing of blood draws paralleled the other studies. Data from the acute oral dosing study are not included because blood was only drawn for 6 h postdosing.

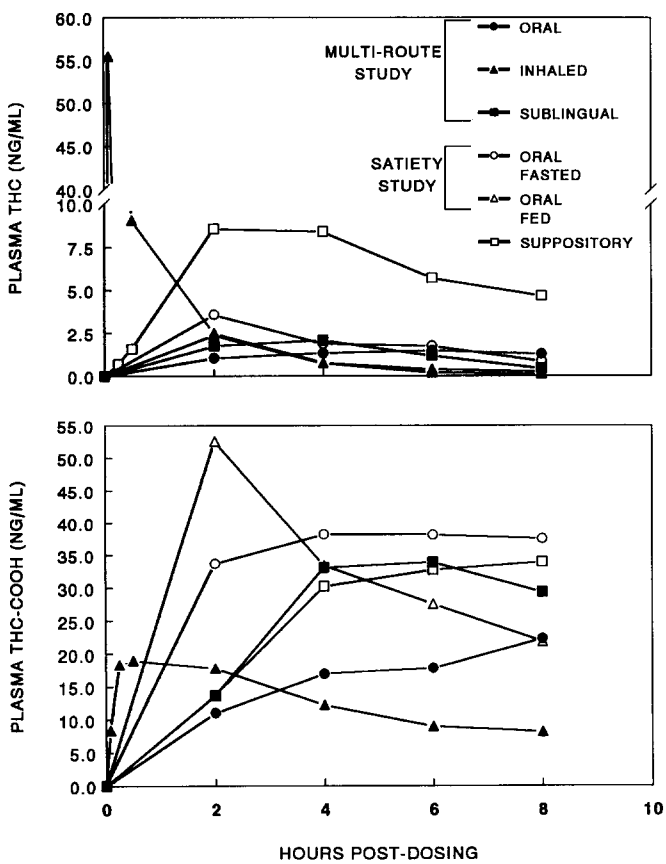

FIG. 1. Mean plasma THC (top panel) and carboxylic acid metabolite (bottom panel) levels following various dosing regimens. Data on suppository dosing is based on two subjects.

Peak plasma THC levels were achieved within 5 min after inhalation of the drug. Peak levels were obtained approximately 2 h postdosing via the other routes. The suppository led to the highest AUC (38.5 ng/ml/min) followed by inhalation (24.5 ± 4.4 ng/ml/min). In contrast, peak levels of the metabolite were observed at different time points—30 min (inhaled), 2 h (oral fed), 4–6 h (oral fasted, sublingual), and 8 h (suppository, oral). The metabolite AUC was highest for the oral-fed (256.6 ± 48.1 ng/ml/min) and fasted (258.6 ± 48.3 ng/ml/min) conditions and lowest following inhalation (102.6 ± 20.8 ng/ml/min).

The AUC-THC values for days 1, 2, and 3 from the chronic study following oral administration were 4.9 ± 2.8, 7.8 ± 3.4, and 8.2 ± 3.8 ng/ml/min and after suppository administration were 16.2 ± 3.5, 15.4 ± 2.4, and 15.7 ± 3.1 ng/ml/min. The AUC-THC-COOH values for days 1, 2, and 3 from the chronic study following oral administration were 82.3 ± 11.8, 145.5 ± 23.0, and 134.5 ± 14.0 ng/ml/min and after suppository administration were 47.7 ± 4.4, 72.7 ± 3.1, and 77.8 ± 7.3 ng/ml/min.

There was a high level of variability in plasma drug levels, especially among subjects after oral drug administration coincident with a small standard breakfast. Thirty-two percent (18/57) and 18% (2/11) of subjects in the acute oral study and oral trial of the multiroute study had no detectable plasma THC or metabolite level in the 4 h following ingestion of the active drug, respectively. With the exception of one subject after oral administration in the fasted state, all other subjects did have a measurable level, but the time course of peak levels and AUC values were highly variable across subjects.

Energy Intake

Mean intake of total kcals, and kcals from breakfast, lunch, snacks, dinner (where available), and the macronutrients are presented in Fig. 2. The energy content of breakfasts in the acute dosing studies were predetermined, but were self-selected in the chronic dosing studies. The top panel includes findings from the acute oral dosing study. Only data from the subset of participants (39/57) who had measurable levels of either the parent drug or metabolite in the immediate 4-h postdosing period are included because they were expected to exhibit the greatest dietary change. The middle panel displays data from the multiroute study and the chronic dosing data are presented in the bottom panel. Data from subjects who reported a "high" during active drug treatment were also analyzed separately and exhibited intakes comparable to the subset of participants with positive drug levels.

No statistically significant differences were observed in any comparisons between active and placebo treatments with a single oral dose (top panel). Sixty percent (34/57) of participants ingested more energy during active treatment. Snacks accounted for more energy than the self-selected lunch during both active and placebo treatments.

Intakes were also similar following acute administration of the drug by oral, inhaled, and sublingual routes (middle panel). Six of eleven subjects ingested more energy after oral

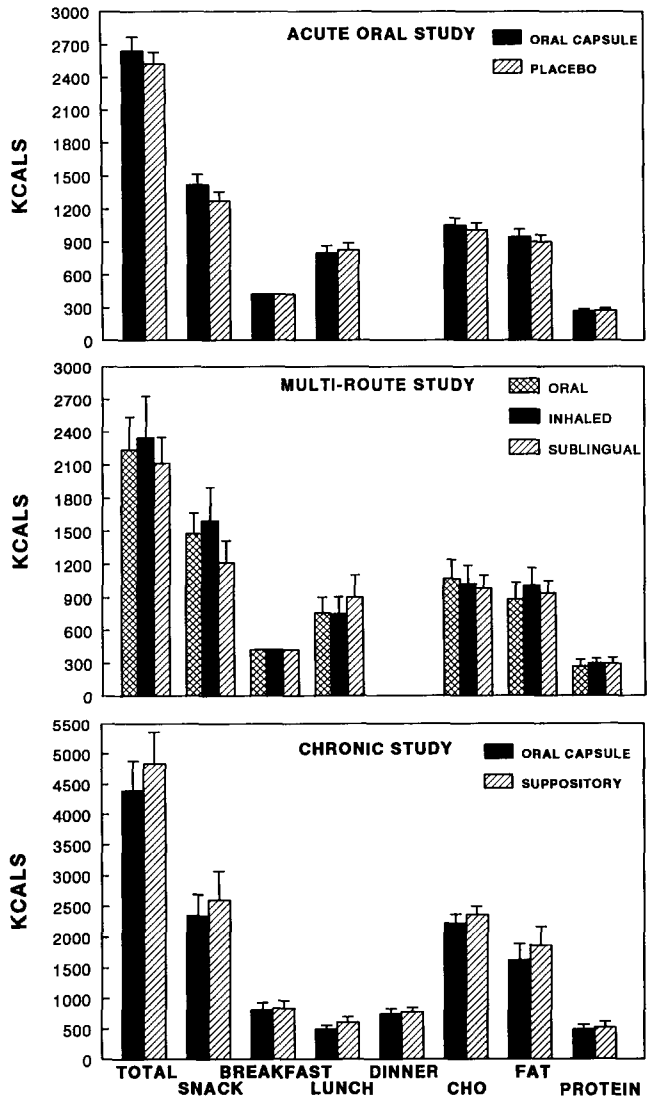

FIG. 2. Mean (±SE) energy and macronutrient intake. Top panel includes data on placebo and active drug treatment days in the 39 subjects with positive parent drug or metabolite levels within the 4 h following active drug administration (top panel). The middle panel includes data from all 11 subjects after acute oral, inhaled, and sublingual drug administration. The bottom panel is comprised of mean daily data from the six subjects dosed for 3 days orally or rectally and includes data from dinner and snacks available for a longer time period relative to the other studies.

dosing compared to smoking, eight ingested more after oral dosing compared to sublingual administration, and six subjects ingested more energy after sublingual dosing compared to smoking. Two of the subjects who reported experiencing a pronounced "high" 2 h following inhalation of THC elected to sleep through lunch and had the lowest daily intakes (830 and 482 kcal). Omitting these subjects, mean energy intake after inhalation of THC was 2719 ± 359 kcal; 481 kcal more than after oral dosing and 603 kcal greater than sublingual dosing effects. Due to the high variance and small sample size, these differences were not statistically significant.

Mean daily intakes did not differ statistically following oral and rectal suppository administration b.i.d. for 3 days (bottom panel). However, there was a substantial increment after suppository dosing compared to oral (4835 kcal vs. 4390 kcal), that stemmed largely from a discrepancy in snacking. Eight of the 10 subjects in the chronic dosing study ingested more energy after suppository dosing compared to the oral dosing condition.

Reported total intakes are higher from the chronic dosing study (bottom panel) because they include energy derived from breakfast, daytime snacks, lunch, dinner, and evening snacks, whereas the latter two sources were not consistently monitored in the acute dosing studies. Self-selected dinner intakes were available from six individuals in the multiroute study, but to increase the power of comparisons of intake between the acute and chronic dosing studies, only energy derived from breakfast, lunch, and snacks are contrasted. Mean daily energy intake during chronic oral dosing was not significantly different from intake after oral placebo or oral active treatments or following inhalation or sublingual drug delivery. In contrast, mean energy intake during suppository treatment (3 day mean = 3726 ± 341 kcal) was significantly greater than intake after both studies using acute oral dosing (acute oral dosing study−2680 ± 114 kcal, $t = 2.91$, $p = 0.026$; multiroute study−2664 ± 301 kcal, $t = 2.34$, $p = 0.037$), as well as oral placebo (2545 ± 96, $t = 3.34$, $p = 0.016$) and sublingual (2542 ± 232, $t = 2.87$, $p = 0.017$) dosing. It was substantially, although not statistically, higher compared to intake after drug inhalation (2770 ± 385, $t = 1.86$, $p = 0.084$). Dinner contributed 576 ± 186, 688 ± 105, and 724 ± 115 kcal to total intakes of the six subjects in the multiroute study after oral, inhaled, and sublingual dosing, values slightly lower than those of subjects in the chronic study (742 ± 88 (oral) and 775 ± 71 (suppository) kcal).

Figure 3 presents data on energy derived from items self-selected from the snack food tray with predominantly sweet, sour, salty, or bitter taste qualities. The top panel again only includes data from the 39 participants with measurable drug levels. In the acute oral study, energy derived from sweet items was significantly higher than that from foods with all other predominant tastes (all $p < 0.01$) and salty items provided more energy than sour or bitter items (all $p < 0.01$). Energy derived from primarily sour and bitter items were comparable. Active drug treatment did not elicit any significant differential effect relative to placebo. In the multiroute study, sweet and salty items contributed more energy than sour or bitter items (all $p < 0.01$), but intakes of energy from sweet and salty items were comparable as were intakes from sour and bitter items. No differences across routes of delivery were statistically significant. In the chronic study, mean daily intake of energy from predominantly sweet items was greater than that from sour and bitter items under both treatment conditions (all $p < 0.05$). Intake of energy from salty items exceeded that from bitter items only during the oral dosing period. Oral and suppository dosing led to similar effects.

Analyses exploring drug influences on items selected from foods grouped as fats, dairy, meats, grains, fruits, vegetables, and snacks also revealed no significant treatment effects in any of the studies. Snack items (e.g., sweet pastries, chocolate candy) were consistently the largest contributors of energy.

Association Between Intake and Both Plasma Drug Levels and Reported "High"

Data on the association between energy intake and plasma drug levels or reported "high" are presented in Table 2. No

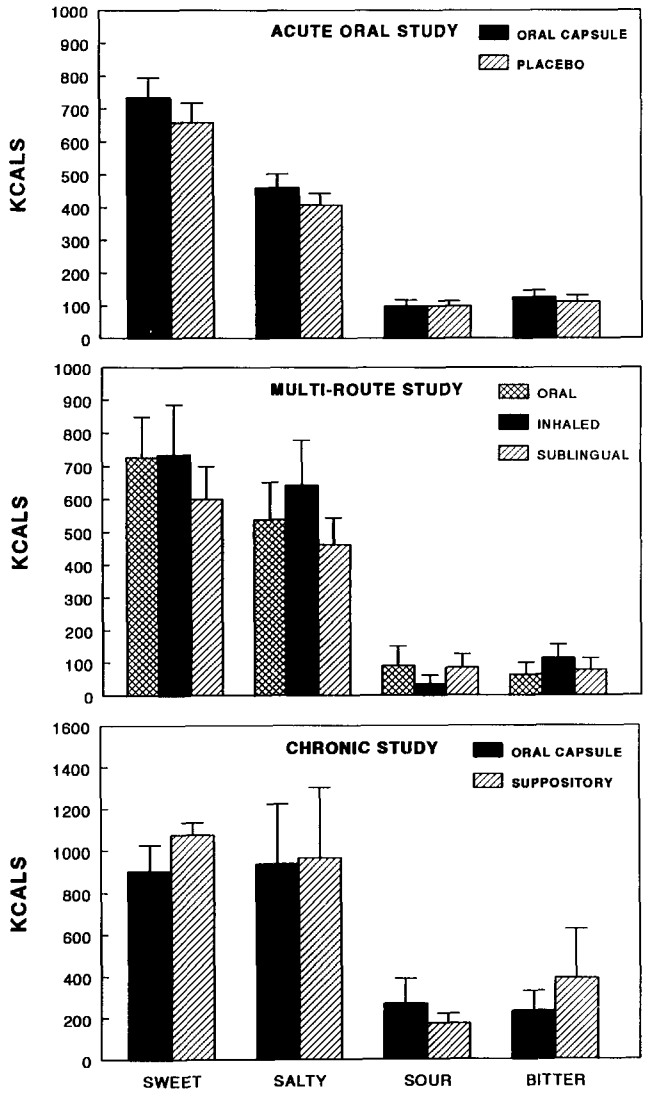

FIG. 3. Mean (±SE) taste quality-related energy derived from items self-selected from a snack tray. Top panel includes data on placebo and active drug treatment days in the 39 subjects with positive parent drug or metabolite levels within the 4 h following active drug administration (top panel). The middle panel includes data from all 11 subjects after acute oral, inhaled, and sublingual drug administration. The bottom panel is comprised of mean daily data from the six subjects dosed for 3 days orally or rectally, and includes data from dinner and snacks available for a longer time period relative to the other studies.

statistically significant correlation was observed between energy intake and AUC drug values, although the correlations tended to be negative in the acute oral study where statistical power was greatest. The correlation between intake and the metabolite/parent drug ratio in the acute oral study was 0.15 and not statistically significant. To control for a potential influence of body weight on the association between intake and plasma drug level, AUC (ng/ml/h)/body weight (kg) ratios (for parent drug and metabolite) were computed and correlated with intake. No significant associations were observed. Energy intake was not significantly related to reported "high" under any condition. However, it should be noted that approximately 20% of participants in the acute oral study who reported little or no "high" during the study day volunteered information that they experienced a "high" later that evening and ate large amounts of food. Plasma drug levels were highest at the final blood draw for only two of these individuals.

Relationship Between Pre- and Posttreatment Food Intake

Energy intake after participants received a single oral dose of active THC either following an overnight fast or consumption of a morning meal is depicted in Fig. 4. Self-selected energy intake was significantly increased ($t = 2.67$, $p = 0.026$) on the study day that did not include the breakfast so that total intake was comparable on both days.

The difference in self-selected energy intake on the fed and fasted days is not attributable to differences in drug levels or degree of induced "high." AUC values were 15.4 ± 3.8 vs. 6.9 ± 2.0 for parent drug and 256.6 ± 48.0 vs. 258.6 ± 48.3 mg/ml/min for the carboxy metabolite on fed and fasted days, respectively, and did not differ significantly. Reported "high" also did not differ significantly between the treatment days.

Associations Between Age and Intake, Plasma Drug Levels, and Reported "High"

The influence of age on various dependent variables was determined only with data from the acute oral study because of its larger sample size. Analyses used intake scores computed as the difference in energy intake between active and placebo treatment days. No significant association was observed between age and difference in total energy intake ($r = 0.11$), reported "high" ($r = -0.11$), AUC for parent drug ($r = 0.02$), or AUC for metabolite levels ($r = -0.06$). The AUC for the drug metabolite was significantly correlated with reported "high" ($r = 0.46$, $p < 0.001$), but for the parent drug this association was substantially weaker ($r = 0.20$, $p > 0.2$).

DISCUSSION

A large anecdotal and descriptive literature [e.g., (3,16, 19,20,28,36)] suggests marijuana stimulates appetite and food intake. However, findings from controlled studies are less compelling. In an early acute oral-dosing study (21), marijuana elicited an increase in consumption of a single test beverage (chocolate milkshake) in fed, but not fasted subjects. The effect was highly variable in both groups with only 7 of 12 subjects exhibiting an increase. Decreased appetite was reported by four fasted and one fed subject. Appetite stimulation has been observed in healthy subjects after smoking marijuana but, again, the results have been variable and sensitive to methodological conditions. One study noted an increased total daily energy intake, but the effect was attributable to increased intake when the drug was smoked communally, no increment was noted when subjects smoked the drug alone (12). A substantive increase in total intake was only apparent in five of the nine subjects. Another study by this group using similar conditions revealed no significant increment in intake (13). Following long-term (i.e., 21–39 days) use of smoked marijuana, energy intake was found to rise during the initial few days and to decline thereafter, suggesting the development of a drug tolerance (17,39). The incidence of reported increased appetite among chronic illicit users is less than 50% (7).

Although not specifically designed to evaluate the appetite-stimulating effects of THC, several clinical trials assessing the antiemetic potential of the drug in cancer patients receiving chemotherapy have also included measures of appetite and

TABLE 2

PEARSON CORRELATION COEFFICIENTS BETWEEN ENERGY INTAKE AND AUC-THC, AUC-COOH, AND MEAN REPORTED "HIGH" IN THE ACUTE ORAL DOSING STUDY (COLUMN 1), MULTIROUTE STUDY (COLUMNS 2-4), SATIETY STUDY (COLUMNS 5 AND 6), AND CHRONIC DOSING STUDY (COLUMNS 7 AND 8)

	Acute Oral Study	Multiroute study			Satiety Study		Chronic Study	
	Oral (n = 57)	Sublingual (n = 11)	Oral (n = 11)	Inhaled (n = 11)	Fed (n = 10)	Fasted (n = 10)	Oral (n = 6)	Suppository (n = 6)
Intake vs. AUC-THC	−0.27	−0.01	0.01	0.14	−0.27	−0.11	−0.39	0.32
Intake vs. AUC-COOH	−0.12	0.51	0.34	0.41	0.48	0.24	0.78	0.50
Intake vs. × high	0.05	−0.32	−0.50	0.62	−0.06	0.18	0.59	0.14

Mean "high" values are means of reported high levels over each treatment day. Data from the chronic dosing study are daily means.

food intake. Results from these studies are best characterized by their high level of variability. Where an overall increase in food intake was noted, the phenomenon was apparent in only about 50% of patients (34). In other studies, patients taking THC reported feeling more hungry than patients on other antiemetics, although there was no significant difference in measured appetite ratings or food intake (10,37). Other studies involving cancer patients receiving chemotherapy have failed to observe a positive effect of THC on appetite [e.g., (6)]. However, evaluation of findings from these clinical trials is problematic since a THC-related enhancement of appetite may have been masked by the concomitant administration of a chemotherapeutic drug that suppressed intake. In addition, it is not possible to ascertain whether positive effects were a direct result of the drug or secondary to an amelioration of nausea and emesis. Patients with anorexia nervosa have also failed to exhibit an increase in food intake after administration of THC (18).

The present series of studies did not reveal a significant effect of acute dosing with THC on total energy intake or energy derived from different food groups or items with various taste qualities. Intakes characterized in these ways were also comparable following repeated dosing (2.5 mg b.i.d. for 3 days) via oral or rectal routes. However, daily energy intakes were higher with chronic dosing. This was statistically significant during suppository treatment relative to all acute dosing studies except the condition where the drug was inhaled.

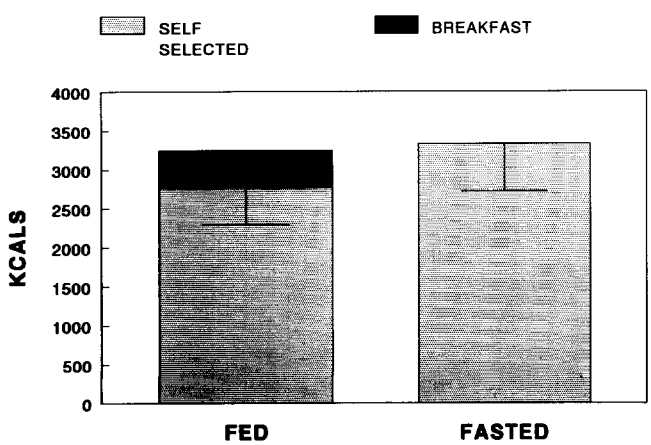

FIG. 4. Mean ± SEM total energy intake of 10 subjects administered THC orally after an overnight fast and following a 455 kcal breakfast.

The fact that snack foods were available to participants several hours longer in the chronic studies may provide a partial explanation for the increment in intake noted in the chronic study. However, intake was not significantly elevated during chronic oral dosing, when the snack tray was also available. It should also be noted that self-selected lunch and dinner meals were higher in energy value during chronic dosing compared to acute.

A "ceiling" effect attributable to the free availability of foods seems an unlikely explanation for the similarity of intakes following acute dosing because daily intakes were substantially higher in the chronic dosing studies. Although the importance of setting on the behavioral effects of THC use has been noted (16,23), an inhibitory effect of the hospital environment on intake is also refuted by the augmentation noted in the chronic study. No daily increment of intake, suggestive of acclimation to the setting, was identified in the chronic study.

A high level of variability in THC absorption and metabolism following oral dosing has been documented (2,38) and could partially explain our failure to note a significant influence of THC on intake in the acute-dosing studies. Over 30% of subjects in the acute oral study had no detectable level of parent drug or metabolite in their plasma within 4 h postdosing. Analyses focusing only on subjects with measurable plasma drug levels also failed to reveal treatment effects. Levels were still highly variable in this group. Inhalation of THC led to more consistent elevations of plasma drug concentration and tended, albeit not significantly, to promote intake.

Although chronic dosing resulted in more consistent plasma drug levels, the impact on intake is uncertain because no statistically significant association was noted between parent drug level and total intake in any of our studies. However, it is noteworthy that in the acute oral study, where statistical power was greatest, the association was inverse. Similar findings have been reported in other studies of healthy marijuana users (15,17) and may be attributable to a sedating effect of the drug when present at a high plasma concentration. Data from a recent clinical study (31) suggest an oral dose of 2.5 mg b.i.d. is optimal for appetite stimulation. This dose is only 5–50% of the level used in all previous work and in our acute dosing studies. The markedly higher energy intakes observed among patients in the chronic studies, especially those administered the suppository, supports the use of a lower dose than

that often used for emetic control. However, the optimal dose for different formulations may vary due to significant differences in the degree and reliability of drug absorption. The suppository led to substantially higher plasma parent drug levels and intake relative to the oral formulation administered at the same dose.

The weak correlation between intake and plasma drug level may also indicate that the parent drug is not the principal mediator of the appetitive effect. The stronger correlations between intake and carboxy metabolite levels suggest this compound or another unmeasured metabolite may contribute to the effect.

Anecdotal reports indicate that marijuana may also alter eating patterns and, in particular, stimulate a desire for sweet items (12,15,20,21). More frequent intake of snack foods accounted for much of the noted increase in total energy intake in several controlled studies (12,13,15). Although not statistically significant, the present data also reveal a larger increment in consumption of energy from this class of foods than others. In one study of six subjects (13), sweet solid snacks were especially targeted. Analysis of the energy derived from snack items with predominantly sweet, salty, sour, and bitter taste notes did not reveal any quality specific effects in the present studies. In neither our work nor other published reports has THC elicited significant shifts in macronutrient intake (12,33) and biochemical indices of nutritional status (e.g., plasma thiamin, pyridoxine, riboflavin, copper, zinc, magnesium) are comparable in marijuana users and nonusers (11).

The mechanism(s) by which THC exerts its behavioral actions are not established. Decreased restraint or inhibition (39) or social facilitation (21) have been proposed. One group noted an increase in energy intake among subjects smoking marijuana in a social setting but not when smoking alone (12). Subsequent work by that group did not confirm this observation (13). Others have noted that increased food intake is highly correlated with experience of a "high" (34), and such a sensation is strongly socially mediated (23). The association between reported "high" and intake was weak in our series of studies. However, approximately 20% of study participants volunteered information that upon returning home after study, they experienced a resurgence of a "high" and ate copiously. The low incidence of appetite stimulation in controlled studies (about 50%) relative to descriptive accounts [e.g., (19,36)] (about 90%) where personal choice dictated use patterns may reflect the importance of social setting in influencing intake and the drugs true potential efficacy for appetite stimulation.

Previous work indicated the satiety status of individuals using the drug could influence intake. One study noted increased intake of a milkshake in subjects administered THC after a meal compared to when the drug was given after an overnight fast (21). However, similar numbers of subjects exhibited increased intake under the fed and fasted conditions. Further, in that study, fed subjects received a lower dose of THC than fasted subjects (mean = 26 mg vs. 32 mg) and, if lower doses more effectively stimulate appetite, this could explain the observation. Another study involving cancer patients did not reveal differences in body weight in patients administered the drug orally either after an overnight fast or after dinner, but noted a higher incidence of adverse side-effects in the fasted state (31). It was hypothesized that this was due to increased drug absorption. The present data do not support such a view because AUC levels in fed and fasted subjects were comparable. An increased daily energy intake could be anticipated in fed subjects because several reports indicate THC-elicited feeding occurs in the absence of hunger (1,15,19,30) and if the drug dampened the satiety mechanism(s), no compensation would be expected for the food taken before or with the drug. However, in our study, subjects tested in both fed and fasted states self-selected significantly less energy on the fed day, and demonstrated very precise compensation for the energy derived from the provided breakfast. These data are not consistent with a view that THC impairs the satiety mechanism.

In antiemetic trials in patients receiving chemotherapeutic agents, THC was associated with a high incidence of disconcerting side effects (e.g., sedation, dizziness, dry mouth), especially among older patients (14,37). THC-related appetite stimulation has been less pronounced in studies of older populations [e.g., mean age = 47 years (37) vs. median of 11 years (10) or mean of 32.5 years (34)] and may be related to age or prior familiarity with THC effects. In the clinical trial failing to note an association between age and appetite or food intake (37), prior experience with the drug was not controlled. The present study included only marijuana-experienced individuals and, over the age range studied (about 20–50 years, mean 31.3 years, slightly lower than that of subjects in the negative clinical trial), no variations in food intake were observed. Thus, our data do not support an interaction between age, albeit of a limited range, and appetitive behavior after THC use.

Aside from a potential benefit of marijuana on increased appetite and quality of life in patients who might be treated with the drug, the primary interest in the appetitive properties of THC lies in its potential to stabilize or promote increased body weight. Several studies of healthy individuals and clinical populations (e.g., patients with cancer or AIDS) document such an effect (17,31,39). However, noted changes of body weight often are not supported by consistent modifications of diet (13,17,39). Drug-induced behavioral changes resulting in decreased energy expenditure have been hypothesized to account for increased weight gain in the absence of increased energy intake (39). Shifts of fluid balance do not account for the findings (17,39). Thus, our failure to document a THC-related increment in food intake should not be interpreted as evidence that THC will be ineffective in the maintenance of adequate body weight in clinical populations.

In summary, the present data demonstrate an appetite-stimulating action of THC in healthy, adult, light marijuana users only when administered at a dose of 2.5 mg b.i.d. by rectal suppository. Comparable oral dosing was less effective. Acute administration of the drug by various routes at levels often used to control nausea and emesis did not elicit an increment in energy intake. Under the conditions of these studies, subject age, gender, hunger status, reported "high," and plasma drug level were not significantly associated with drug effects on food intake. However, different results may be obtained under varying conditions (i.e., a social setting conducive to positive drug-related effects on psychological and behavioral measures) or with selected clinical populations.

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