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ORIGINAL INVESTIGATION

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Comparison of the subjective effects of Δ^9-tetrahydrocannabinol and marijuana in humans

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Abstract *Rationale:* There has been controversy about whether the subjective, behavioral or therapeutic effects of whole plant marijuana differ from the effects of its primary active ingredient, Δ^9-tetrahydrocannabinol (THC). However, few studies have directly compared the effects of marijuana and THC using matched doses administered either by the smoked or the oral form. *Objective:* Two studies were conducted to compare the subjective effects of pure THC to whole-plant marijuana containing an equivalent amount of THC in normal healthy volunteers. In one study the drugs were administered orally and in the other they were administered by smoking. *Methods:* In each study, marijuana users (oral study: *n*=12, smoking study: *n*=13) participated in a double-blind, crossover design with five experimental conditions: a low and a high dose of THC-only, a low and a high dose of whole-plant marijuana, and placebo. In the oral study, the drugs were administered in brownies, in the smoking study the drugs were smoked. Dependent measures included the Addiction Research Center Inventory, the Profile of Mood States, visual analog items, vital signs, and plasma levels of THC and 11-nor-9-carboxy-THC. *Results:* In both studies, the active drug conditions resulted in dose-dependent increases in plasma THC levels, and the levels of THC were similar in THC-only and marijuana conditions (except that at the higher oral dose THC-only produced slightly higher levels than marijuana). In both the oral study and the smoking study, THC-only and whole plant marijuana produced similar subjective effects, with only minor differences. *Conclusion:* These results support the idea that the psychoactive effects of marijuana in healthy volunteers are due primarily to THC.

Keywords Cannabinoid · Tetrahydrocannabinol · THC · *Cannabis sativa* · Marijuana

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Introduction

The medical use of marijuana (*Cannabis sativa*) has generated considerable controversy and public discussion, and raised a number of interesting scientific questions (Joy et al. 1999; Iverson 2000). One of the central controversies surrounding the medical use of marijuana, and one highlighted by the recent Institute of Medicine report on marijuana and medicine (Joy et al. 1999), is whether the effects of the whole plant are different from the effects produced by its primary active ingredient, Δ^9-tetrahydrocannabinol (THC). Some patients claim that marijuana is more effective than THC for a variety of symptoms, including nausea and vomiting, wasting syndrome, and muscle spasticity (Grinspoon and Bakalar 1997; Joy et al. 1999). However, most of these claims are based on patient reports and surveys, and have not been addressed in carefully controlled laboratory studies.

One complication in evaluating the clinical claims about marijuana versus marketed forms of THC is that marijuana is usually smoked, whereas the therapeutic forms of THC are taken orally. These differences in route of administration probably account for some of the apparent differences between smoked marijuana and oral THC. Smoking produces a faster onset of effects and higher plasma levels of drug, which may lead to a more rapid and effective symptom relief for patients. Comparisons of the smoked and oral forms are complicated by the subjects' expectancies and their prior history with smoked marijuana (Kirk et al. 1998). Furthermore, different routes of administration may also result in different levels, or ratios, of cannabinoids and their

metabolites, which could affect responses. For example, Wall and colleagues found that oral and intravenous administration of THC resulted in different ratios of parent THC to active metabolites (Wall and Perez-Reyes 1981; Wall et al. 1983). For these reasons, it is important to compare the effects of whole plant marijuana and THC alone at matched doses, within the same route of administration.

THC is known to be the primary active cannabinoid in the marijuana plant (Martin 1986). However, whole plant marijuana also contains more than 60 other cannabinoid constituents including Δ^8-tetrahydrocannabinol, cannabinol, and cannabidiol (Turner et al. 1980), some of which may contribute either directly or indirectly to the effects of marijuana. For example, Δ^8-tetrahydrocannabinol produces physiological and behavioral effects that are similar to THC (Hollister and Gillespie 1973; Levander et al. 1974; Agurell et al. 1976). Cannabinol and cannabidiol do not appear to have potent THC-like effects alone (Perez-Reyes et al. 1973; Karnoil et al. 1974, 1975; Dalton et al. 1976; Musty et al. 1976), but these cannabinoids can alter the effects of THC (Hollister 1973; Karnoil et al. 1974, 1975; Hollister and Gillespie 1975; Dalton et al. 1976; Musty et al. 1976; Zuardi et al 1982). Moreover, cannabinol and cannabidiol may have other CNS or therapeutic effects independent of marijuana-like or THC-like psychological effects (Cunha et al. 1980; Carlini and Cunha 1981). For example, it has been suggested that cannabidiol may decrease the anxiety elicited by THC so that users experience more pleasurable effects from the whole plant (Karniol et al. 1974). The focus of this series of studies was to assess the possibility that other cannabinoids present in marijuana contribute to its subjective effects. Subjective effects were selected as the dependent measures because they provide a sensitive and reliable measure of central drug effects, which can be assessed in healthy volunteers whose responses are not complicated by medical conditions. Differential profiles of subjective effects may suggest that the drugs also differ on other measures, including behavioral or therapeutic effects.

Thus, the present project compared the effects of THC to whole-plant marijuana. The project consisted of two separate studies involving two different routes of administration. In the first study, the drugs were administered orally in chocolate brownies (oral study), and in the second study, the drugs were smoked (smoking study). In both studies, subjects were tested under five conditions: placebo, low and high doses of whole-plant marijuana, and low and high doses of THC only (i.e. THC-laced placebo marijuana). The whole-plant and THC only conditions were matched for THC content, allowing a direct comparison of the effects of whole plant marijuana to THC. Thus, differences in the effects of the whole plant marijuana compared to THC alone would suggest that other cannabinoid constituents contribute to the effects of whole plant marijuana.

Table 1 Subject demographic and drug use summary

Variable	Oral (*n*=12)	Smoking (*n*=13)
Sex (*n*)		
Female/male	5/7	6/7
Age (years)		
Range	18–31	19–26
Mean±SD	23±4	21±2
Weight (lb; mean±SD)	150±22	144±16
Race		
Caucasian	8	8
African-American	3	2
Asian or Native American	1	3
Marital status (*n*; not married)	12	13
Education (*n*)		
Partial college	6	9
College degree	7	2
Full time student (*n*)	8	9
Current recreational drug use		
Alcohol (mean±SD; drinks/week)	5±3	5±3
Caffeine (mean±SD; drinks/week)	7±6	12±9
Cigarettes (*n*; >2.5 cigarettes/day)	5	6
Marijuana (*n*; >0.5 cigarettes/week)	11	12
Lifetime recreational drug use		
Stimulants (*n*; ever used)	8	10
Tranquilizers (*n*; ever used)	1	3
Hallucinogens (*n*; ever used)	9	11
Opiates (*n*; ever used)	4	8
Marijuana		
Used 10–50 times (*n*)	4	3
Used >50 times	8	10
Inhalants (*n*; ever used)	8	6

Materials and methods

These studies were approved by the Institutional Review Board of the University of Chicago and were conducted ethically in accordance with the Helsinki Declaration of 1964 (revised 1989) and the National Advisory Council on Drug Abuse Recommended Guidelines for the Administration of Drugs to Human Subjects.

The subjects were recruited from the community through posters and newspaper advertisements. Candidates were initially screened in a brief telephone interview to ensure they had at least a high school degree, were native English speakers, and had a body mass index in the range of 19–26 kg/m^2. Qualified individuals completed questionnaires regarding their health and psychiatric symptomatology (SCL-90; Derogatis 1983). To ensure that potential subjects did not have a current or previous psychiatric disorder and were physically healthy, they underwent a psychiatric interview (DSM-IV; American Psychiatric Association 1994), received an electrocardiogram, and had a physical examination.

Prior to participation in the study, subjects attended an orientation session to provide written informed consent and to familiarize them with the experimental procedures and dependent measures. The consent form stated that the purpose of the experiment was to investigate the effects of drugs on mood and behavior. The consent form indicated that the subjects might receive a stimulant, sedative, antihistamine, antidepressant, cannabinoid, or placebo, and listed potential side effects of these drug types. Subjects were instructed to refrain from other drug use, but to maintain their normal level of caffeine and nicotine use prior to each session. Subjects were instructed not to eat after 1600 hours on the day of each session. After completing the study, subjects were debriefed and paid for their participation.

Table 2 Study design

Oral study (*n*=12)	Smoking study (*n*=13)
Placebo brownie (P)	Placebo cigarette (P)
Low dose marijuana brownie (MjLow)	Low dose marijuana cigarette (MjLow)
High dose marijuana brownie (MjHigh)	High dose marijuana cigarette (MjHigh)
Low dose THC brownie (THCLow)	Low dose THC cigarette (THCLow)
High dose THC brownie (THCHigh)	High dose THC cigarette (THCHigh)

Subjects

The participants were healthy volunteers who had prior experience with marijuana. To participate, subjects had to report use of marijuana or hashish at least once in the last 2 months and at least 10 times in their lifetime. A summary of the demographics and drug use history of the subjects are presented in Table 1.

Design

Both studies utilized a placebo-controlled, within-subject, crossover design. Each subject participated in five experimental conditions as shown in Table 2.

Subjects participated in the five conditions in randomized order under double-blind conditions, and sessions were conducted at 1-week intervals. The amount of THC in the Low and High dose THC conditions in both studies was matched to the amount of THC in the corresponding Low and High dose marijuana conditions, as described below.

Procedure

Experimental sessions were conducted from 1730 to 2330 hours in the General Clinical Research Center (GCRC) at The University of Chicago Hospitals. Upon arrival for each session, subjects provided a urine sample for drug and pregnancy screening. To verify that each subject was ethanol-free, blood alcohol level was estimated by breath alcohol level (BAL) using an Alco-Sensor III hand-held breathalyzer (Intoximeters, Inc., St Louis, Mo., USA). At 1745 hours, a nurse inserted a catheter into a forearm vein and obtained a baseline blood sample. The nurse recorded baseline vital signs and assessed psychomotor performance, and subjects completed a series of baseline mood and drug effect questionnaires (see dependent measures below). At 1800 hours, subjects in the oral study ingested a chocolate brownie containing the drug with 100 ml water, and completed questionnaires and other tests (including blood samples) 30, 60, 90, 120, 150, 180, 240, and 300 min after this. Subjects in the smoking study were escorted to the Human Behavioral Pharmacology Laboratory (a 3-min walk) immediately after baseline (hour 0) determinations. Subjects smoked their cigarettes according to a paced puff procedure in which they smoked two half cigarettes. Each half cigarette was placed in a plastic cigarette holder from which the filter had been removed. Subjects were instructed to draw on the cigarette for 5 s, hold their breath for 10 s, and then exhale. This procedure was repeated at 1-min intervals. It took the subjects an average of 17 puffs to smoke both half cigarettes. After completing the smoking procedure, subjects returned to the GCRC for the remainder of the session, where they completed additional measures (blood samples, vitals signs, and subjective effect data) at 5, 15, 30, 45, 60, 90, 120, 150, 210, and 300 min after completion of smoking. ARCI and POMS questionnaires were not completed at 15 and 30 min after smoking.

In both studies, a choice of snack foods was provided at 2100 hours, and subjects' consumption was recorded. At the last time point, 300 min, subjects completed an end of session questionnaire in addition to the other dependent measures. Subjects were tested individually. At times when no dependent measures were being collected, subjects were allowed to engage in recreational activities such as watching television or movies, reading, and playing games. However, they were not allowed to work or study during the session. Following each experimental session, subjects were transported home.

Dependent measures

Blood pressure and heart rate were monitored using a Dinamap vital signs monitor Model 1846 (Critikon Inc., Tampa, Fla., USA). Temperature was assessed using an aural infrared thermometer Model LTX-1 (Exergen Corp., Newton, Mass., USA). A nurse assessed respiration rate. Plasma levels of Δ^9-THC and 9-COOH-THC were determined by radioimmunoassay (Research Triangle Institute, N.C., USA). The food intake for each subject on each session was recorded and the KCAL, carbohydrate, protein, and fat content of the foods calculated based on values from Nutritionist IV (First DataBank, Inc., San Bruno, Calif., USA). In the smoking study, the number of puffs and expired CO were monitored during the smoking procedure. Expired CO was monitored using an EC50 Micro III Smokerlyzer (Bedford Scientific, Medford, N.J., USA).

Psychomotor performance was determined using the Digit Symbol Substitution Test (DSST) of the Wechsler Adult Intelligence Test (Wechsler 1958). The DSST is a paper and pencil test for which subjects are required to transpose a series of symbols for numbers as quickly and accurately as possible. The data from this test consists of the number of correct symbol transpositions during a 60 s trial.

Mood and drug effects were evaluated using pencil and paper questionnaires. Mood states were assessed using an experimental version of the Profile of Mood States (POMS; McNair et al. 1971; Johanson and Uhlenhuth 1980). The POMS consists of 72 adjectives commonly used to describe momentary mood states. Subjects rate from 0 (not at all) to 5 (extremely) the extent to which each adjective describes how they feel at that moment. The items on the POMS have been factor analyzed to yield eight mood state scales: Anger, Anxiety, Confusion, Depression, Elation, Fatigue, Friendliness, and Vigor. In addition the POMS has two intuitively derived scales: Arousal [(Anxiety+Vigor)–(Fatigue+Confusion)] and Positive Mood (Elation-Depression). Subjective drug effects were determined using a 53-item version of the Addiction Research Center Inventory (ARCI; Martin et al. 1971), which was comprised of some of the original 49 items plus 4 items specific to marijuana (Chait et al. 1985). The new items were "I have difficulty in remembering", "My mouth feels very dry", "I notice that my heart is beating faster", and "My thoughts seem to come and go". The resulting 53-item ARCI contained true or false statements sensitive to the effects of several drug classes. It had six empirically derived scales: the Marijuana (M) scale, the Amphetamine (A) and Benzedrine Group (BG) scales that are indices of stimulant-like effects, the Morphine-Benzedrine Group (MBG) scale that is a measure of euphoria, the Pentobarbital-Chlorpromazine-Alcohol Group (PCAG) scale which is an index of sedation, and the Lysergide (LSD) scale that is a measure of dysphoria and somatic symptoms.

Subjects also rated subjective drug effects using a series of visual analog scales (VAS; Folstein and Luria 1973) and a drug effects questionnaire (DEQ). The VAS consists of six adjectives and visual analog scales: "stimulated", "high (as in drug high)", "anxious", "sedated", "down", and "hungry". Subjects were required to rate on 100 mm lines the extent to which they feel each adjective from "not at all" on the left to "extremely" on the right. The DEQ

contained four 100 mm visual analog scales that the subjects used to mark their response the following questions: 1) Do you feel any drug effects, rated from “none at all” to “a lot”, 2) Do you like the effects you are feeling now, rated from “dislike” to “like very much”, 3) Are you high, rated from “not at all” to “very”, and 4) Would you like more of what you consumed, right now, rated from “not at all” to “very much”, used to assess how much the subjects want the drug.

Drugs

Oral study

The brownies were prepared according to a standardized recipe (Cone et al 1988; see below), using marijuana and placebo cigarettes obtained from the National Institute on Drug Abuse (NIDA). In the two whole plant marijuana conditions, the brownies were made using one-half (MjLow) or one (MjHigh) 800 mg marijuana cigarettes. These cigarettes have a THC content of 2.11±0.06% (w/w), as well as 0.30% cannabinol and 0.05% cannabidiol. Thus, the estimated dose of THC in these cigarettes was 8.4 mg in the low dose condition and 16.9 mg in the high dose condition. Brownies for the placebo (P) condition were made using placebo marijuana cigarettes from which all cannabinoids have been removed. In the THCLow and THCHigh conditions, the brownies were made using either a half or a whole placebo cigarette that had been laced with THC, at a concentration matching the THC content of the active marijuana conditions. These cigarettes were laced by injecting 16.9 mg of the synthetic THC, dronabinol, dissolved in ethanol, along the length of the cigarette. THC-only cigarettes were prepared by one of the authors (MAES). For comparison, clinical doses of oral THC for appetite stimulation and antiemetic effects range from 2.5 to 20 mg per day.

The brownies were prepared by the dietary staff in the GCRC, and checked for THC content after baking. To prepare the cigarettes for baking, the plant material from the cigarettes for nine doses of each condition was ground to a fine powder. To equate the amount of plant material in each condition, placebo cigarettes were used so that the amount of plant material always equaled nine cigarettes in each batch of powder. This powder was then added to a chocolate brownie mix, Duncan Hines double-fudge brownie mix. The brownie mix was prepared according to the manufacturer’s instructions but the amounts of the ingredients were standardized to 645 g dry mix, 30 g fudge, 100 g egg, 65 g water, and 40 g oil. The wet batter was weighed out into nine equal portions prior to baking and each portion baked in an individual muffin container. To confirm that the THC content of the brownies reached expected values and was matched across conditions, THC was extracted from the brownies and analyzed by gas chromatography and mass spectroscopy. The amount of THC in each of the five types of brownies was determined in two batches as shown in Fig. 1.

Smoking study

The cigarettes used were from the same batch as the marijuana and placebo cigarettes in the oral study. For the MjLow condition, subjects smoked one half of a standard NIDA marijuana cigarette and one half of a placebo cigarette; for the MjHigh condition, subjects smoked two halves of a marijuana cigarette [THC 2.11±0.06% (w/w)]. Therefore, the subjects smoked the equivalent of 8.4 mg in the MjLow conditions and 16.9 mg in MjHigh condition. In the P condition, subjects smoked two halves of a placebo marijuana cigarette. In the THC only conditions, the subjects smoked placebo cigarettes that had been laced with THC, at a concentration matching the THC content of the active marijuana conditions. Again, the subject smoked one half of a THC laced cigarette and one half of a placebo cigarette in the low dose condition (THCLow). For all the conditions, each cigarette half was rolled in an additional piece of opaque, purple, cigarette paper with a grape aroma to blind the subjects and research staff to the drug condition. The order of administration of the two half-cigarettes in the low dose condition was random, because of the blinding.

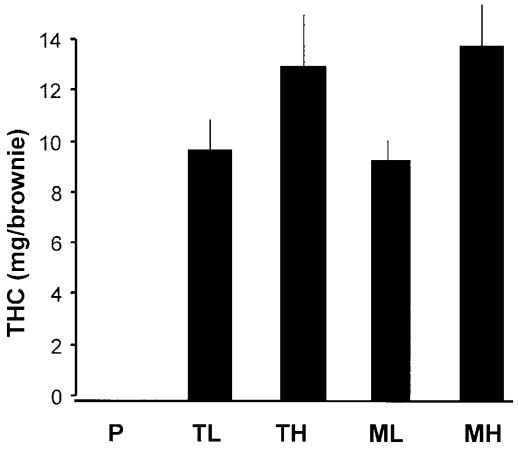

Fig. 1 Mean (±SEM) THC content (mg) of samples of brownies containing placebo (*P*), a low dose of THC (*TL*), a high dose of THC (*TH*), a low dose of marijuana (*ML*) or a high dose of marijuana (*MH*). Each mean is based on two samples obtained from the middle of the baking tin of two batches

Data analysis

Data from the oral study and the smoking study were analyzed separately. In each Study we first determined the effects of THC and marijuana on each measure, using two-factor analysis of variance (ANOVA) with factors dose (placebo, low, high) and, if appropriate, time. This analysis was conducted to confirm that the drugs had their expected effects, to assess the magnitude of the effects and to determine which if any of the effects were dose-related. Separate analyses were conducted for each dependent measure. Then, using separate two-way ANOVAs (drug condition and time) for each of the two doses, the marijuana condition was compared to the THC alone condition. Thus, in one analysis THC-Low was compared to MjLow and in another analysis THCHigh was compared to MjHigh. These were the comparisons of primary interest in the study. Significant main effects and interactions were examined post-hoc using the Fisher least significant difference test. The significance level for all statistical tests was set at $P<0.05$.

A potency analysis was conducted for the measure of drug “high” (DEQ) for the two doses tested in the oral study. To do this, the “high” rating for each subject was plotted against the plasma level of THC to produce a concentration versus response curve and (thereby) a response index. The analysis provided a measure of “high” ratings in terms of ng THC per ml plasma.

Results

Oral study

Plasma THC and 11-nor-9-COOH-THC

Plasma levels of THC associated with each condition are shown in Fig. 2. Both THC and marijuana produced significant dose-dependent increases in plasma THC (Table 3), beginning one hour after ingestion of the brownie. Plasma levels of the conjugated THC metabolite, 11-nor-9-carboxy-THC, also increased dose dependently after ingestion of either THC or marijuana brownies

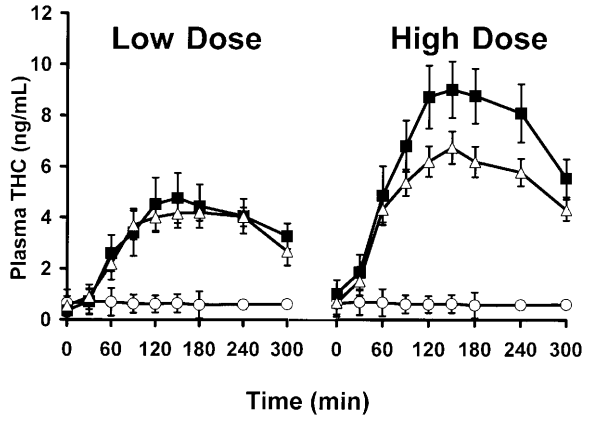

Fig. 2 Mean plasma THC levels over time after oral administration of THC (*solid squares*) and marijuana (*shaded triangles*) or placebo (*open circles*). Low dose conditions are on the *left*, high dose conditions are on the *right*. Means are based on data from 12 subjects, error bars represent SEM

Table 3 Oral study. Significant *F* values (ANOVA) for main effects of dose (P, THCLow, THCHigh or P, MjLow, MjHigh) and interactions of dose×time (time within session). The drug(s) increased scores on all measures except the BG scale of the ARCI, on which scores decreased

Dependent measures	THC		Marijuana	
	Dose	Dose×time	Dose	Dose×time
DEQ				
Feel	19.54***	3.65***	12.16***	2.30**
High	13.55***	3.56***	8.47**	
Want			3.62*	
Like	5.72**			
ARCI				
Marijuana	9.72***	3.93***	3.66*	2.12**
A		2.77***		
BG	5.15*		5.02*	
MBG		2.08*		
PCAG	8.85**	2.24**	6.68**	
LSD	8.57**			
VAS				
Sedated			6.57**	
Hungry			3.83*	
Drowsy			6.52**	
Tired			4.01*	
Vitals				
Heart Rate		2.50**		
THC	57.71***	17.66***	44.36***	25.80***
11-nor-9-COOH-THC	30.64***	22.93***	28.99***	22.41***

*P<0.05, **P<0.01, ***P<0.001

(data not shown). For both THC and marijuana conditions the increases in plasma concentration of 11-nor-9-carboxy-THC began 1.5 h after drug ingestion, and rose and declined in accordance with the THC levels, with a slight delay. Five subjects had very low but detectable levels of THC and 11-nor-9-carboxy-THC on one or more occasions at baseline. However, there was no systematic relationship between subjects' pre-session

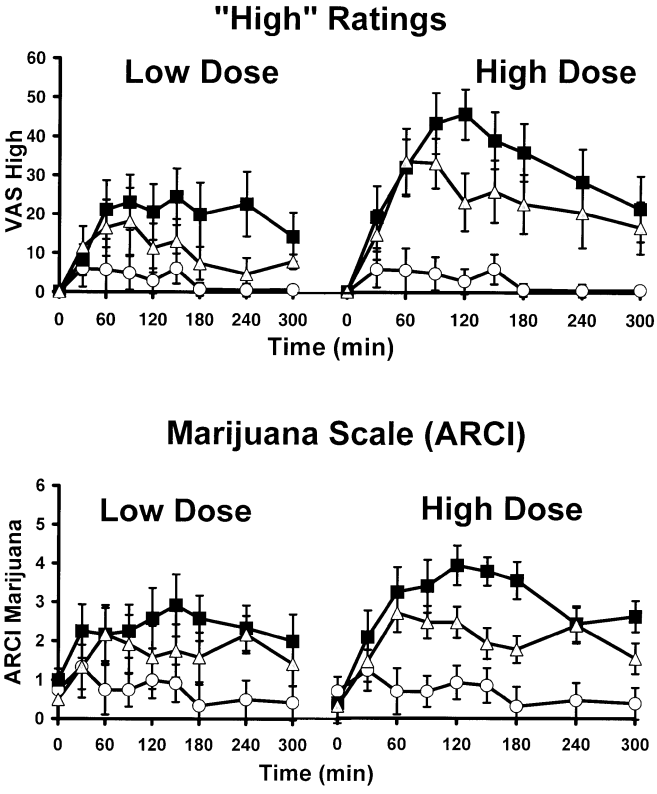

Fig. 3 Mean "high" ratings (*VAS*) and Marijuana scale (*ARCI*) scores over time after oral administration of THC (*solid squares*) and marijuana (*shaded triangles*) or placebo (*open circles*). Low dose conditions are on the *left*, high dose conditions are on the *right*. Means are based on data from 12 subjects, error bars represent SEM

plasma concentrations of THC and the treatment they received on their previous session.

At the lower dose, the plasma THC and 11-nor-9-carboxy-THC concentrations in the THC only and marijuana conditions were well matched. However, at the higher doses, the concentrations of THC and 11-nor-9-carboxy-THC were significantly different [$F(8,88)=3.08$, $P<0.01$ and $F(8,88)=3.14$, $P<0.01$, respectively]. Post-hoc comparisons indicated that higher levels were attained in the THCHigh condition compared to the MjHigh condition. This difference began 90 min after ingestion of the brownie (180 min for 11-nor-9-carboxy-THC) and persisted throughout the session.

Drug effects

THC and marijuana produced similar, prototypic marijuana-like subjective effects (Table 3). Both THC-only and marijuana dose-dependently increased ratings of feeling a drug effect and experiencing a drug high (DEQ), and increased ARCI Marijuana scale scores (Fig. 3). Both THC-only and marijuana increased measures of sedation (Table 3), dose-dependently elevating scores on the ARCI PCAG scale, and, at the higher doses, both drugs decreased ARCI BG scale scores.

The high dose of marijuana increased ratings on VAS items of "Sedated", "Drowsy", and "Tired", but neither dose of THC had these effects. Interestingly, the THC-High condition induced a small increase in one measure of stimulant effects, the ARCI A scale, as well as an increase on the ARCI MBG scale, indicative of euphoria. The THCHigh condition also produced a significant increase on the ARCI LSD scale, indicative of dysphoria.

Neither THC alone nor marijuana had appreciable effects on physiological or behavioral measures (Table 3). Neither drug affected blood pressure, temperature, and respiration. Neither the MjLow nor the MjHigh conditions increased heart rate. There was an effect of THC on heart rate, but this was attributable to lower baseline heart rates on the THCLow session. Both THC alone and marijuana induced small increases in KCAL, carbohydrate, protein, and fat intake, but none of these reached statistical significance. Marijuana had no effect on DSST performance. THC decreased DSST scores at 180 and 300 min, but there were also unexplained differences in DSST performance at baseline, making these results difficult to interpret.

THC versus marijuana comparisons

THC differed from marijuana on only a few measures and only at the higher doses. On the DEQ measure of feeling a drug effect, subjects reported a greater response on the THCHigh condition compared to the MjHigh condition [main effect of drug $F(1,11)=5.07$, $P<0.05$]. This is consistent with the higher plasma levels attained in the THCHigh condition. Similarly, scores on the ARCI A scale were higher in the THCHigh condition than the MjHigh condition, from 60 min until 150 min after drug ingestion [drug×time interaction $F(8,88)=3.59$, $P<0.01$], and scores on the ARCI LSD scale were higher in the THCHigh than MjHigh condition [main effect of drug [$F(1,11)=11.94$, $P<0.01$].

Potency estimates could not be calculated for several subjects (in one or both conditions) because of data variability. At the low dose, the mean potency estimate for the THCLow was 10.65 units of high per ng of THC in plasma (SD 4.35; $n=6$) and for MJLow it was 8.46 (SD 5.36; $n=6$). At the high dose, the mean potency estimate for THCHigh was 9.83 (SD 3.61; $n=9$) and for MJHigh was 7.42 (SD 3.59; $n=9$). The potency of THC and MJ was not significantly different at either dose.

Smoking study

Plasma THC and 11-nor-9-COOH-THC

The time-course of plasma THC levels following smoking for each condition is shown in Fig. 4. Both THC and marijuana produced significant dose-dependent increases in plasma THC (Table 4), which were highest immediately after smoking and declined thereafter. Plasma levels of the conjugated THC metabolite, 11-nor-9-carboxy-THC, also increased dose dependently after smoking either THC or marijuana (data not shown). Again, plasma concentrations of 11-nor-9-carboxy-THC were similar to the THC concentrations, but decreased more slowly compared to THC (data not shown). Eleven subjects had very low but detectable levels of THC and 11-nor-9-carboxy-THC on one or more occasions at baseline, before any drug was administered. However, there was no systematic relationship between subjects' pre-session plasma concentrations of THC and the treatment they received on their previous session.

Based on the plasma THC and 11-nor-9-carboxy-THC concentrations, the THC only and marijuana doses

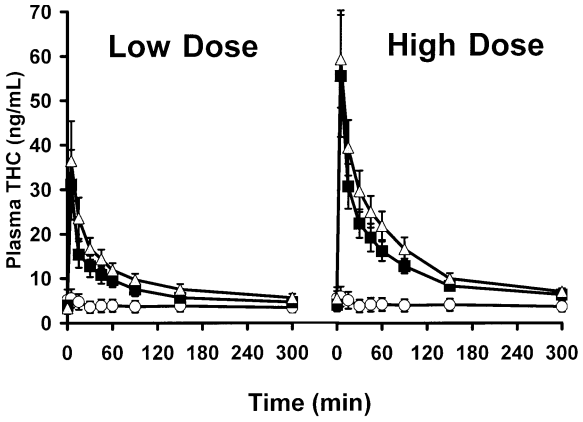

Fig. 4 Mean plasma THC levels over time after smoked administration of THC (*solid squares*) and marijuana (*shaded triangles*) or placebo (*open circles*). Low dose conditions are on the *left*, high dose conditions are on the *right*. Means are based on data from 13 subjects, error bars represent SEM

Table 4 Smoking study. Significant *F* values (ANOVA) for main effects of dose (P, THCLow, THCHigh or P, MjLow, MjHigh) and interactions of dose×time (time within session). The drug(s) increased scores on all measures except the BG scale of the ARCI, on which scores decreased

Dependent measures	THC		Marijuana	
	Dose	Dose×time	Dose	Dose×time
DEQ				
Feel	14.00***	5.63***	22.89***	7.67**
High	12.07***	5.32***	24.82**	7.11
Want			4.76*	2.02**
ARCI				
Marijuana	4.57***	4.29***	6.60**	5.00***
BG			3.93*	
LSD	4.37*	4.12***	5.36*	3.29***
VAS				
Tired		2.17**		
POMS				
Confusion		1.71*		
Vitals				
Heart Rate		2.48**	4.61*	5.03***
Diastolic BP				1.99*
THC	57.71***	17.66***	44.36***	25.80***
11-nor-9-COOH-THC	30.64***	22.93***	28.99***	22.41***

*$P<0.05$, **$P<0.01$, ***$P<0.001$

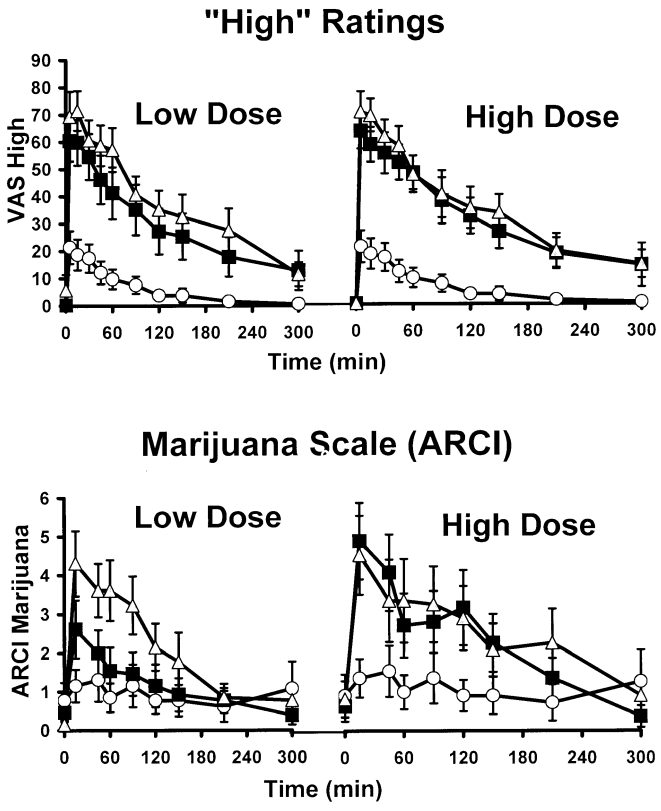

Fig. 5 Mean "high" ratings (*VAS*) and Marijuana scale (*ARCI*) scores over time after administration of smoked THC (*solid squares*) and marijuana (*shaded triangles*) or placebo (*open circles*). Low dose conditions are on the *left*, high dose conditions are on the *right*. Means are based on data from 13 subjects, error bars represent SEM

were well matched. There were no significant differences between the THC and marijuana conditions at either dose.

Drug effects

As in the oral study, THC and marijuana elicited an array of typical marijuana-like subjective effects (Table 4). However, the effects were evident on fewer measures. Both THC and marijuana increased subjects' reports of feeling a drug effect and experiencing a drug high compared to the P condition (Fig. 5). Interestingly, however, these effects were not dose dependent. THC and marijuana did show dose-dependence on other measures. Both THC and marijuana induced dose-dependent increases in scores on the ARCI LSD and Marijuana scales, and in heart rate.

Unlike the oral study, there were few effects of either THC or marijuana on measures indicative of sedation after smoking. The only sedative-like effects were an increase in VAS ratings of "tired" in the THCLow condition, and a decrease in ARCI BG scores in the MjHigh condition. Smoked THC also produced induced a small, dose-dependent increase in scores on the POMS Confusion scale.

THC versus marijuana comparisons

There were minimal differences between the THC and marijuana conditions. Subjects reported a slightly greater increase in VAS ratings of feeling a drug effect in the MjHigh condition compared to the THCHigh condition [main effect of drug; $F(1,12)=5.05$, $P<0.05$]. However, there were no significant differences between the two high dose conditions for any other dependent measure. At the lower dose, the MjLow resulted in a significantly greater increase in heart rate than the THCLow condition at 15 and 45 min after smoking [drug×time interaction; $F(8,96)=3.27$, $P<0.01$]. Scores on the ARCI Marijuana scale and on the POMS Confusion scale were significantly higher in the MjLow condition than the THCLow condition [drug×time interaction: $F(8,96)=3.75$, $P<0.001$; main effect of drug: $F(1,12)=4.84$, $P<0.05$].

Discussion

THC and marijuana in both the smoked and oral form produced similar, dose-dependent subjective effects, and there were few reliable differences between the THC-only and whole-plant marijuana conditions. Both THC and marijuana produced prototypic marijuana-like subjective effects, including increases in ratings of feeling a drug effect, increases on the ARCI Marijuana scale, and increases on several measures of self-reported sedation. Many of these effects were dose-dependent, for both the THC and marijuana, and the effects were similar in the studies involving the oral and the smoked routes. The concentrations of THC in the THC-only and marijuana conditions were closely matched. Notably, however, there were very few systematic differences between THC and marijuana at matched doses, in either the oral study or the smoking study, and the potency analysis in the oral study revealed no difference. Thus, with these standardized marijuana cigarettes, other cannabinoids present in the marijuana plant did not alter the subjective effects of marijuana. It is not clear whether the measures obtained in this study, i.e. self-reported subjective effects of the drugs, correspond with the drug's other effects, including their efficacy in clinical settings. Although these findings do not support some patients' reports that the effects of marijuana are different from the effects of THC (Grinspoon and Bakalar 1997; Joy et al. 1999; Iverson 2000), the possibility remains that whole plant marijuana and THC alone differ on other outcome measures more relevant to clinical entities (e.g. spasticity or neuropathic pain).

Previous studies comparing smoked marijuana and oral THC in the form of dronabinol or nabilone, ignoring the differences in route of administration, have yielded mixed results. Two studies failed to find substantive qualitative differences in the subjective effects of smoked marijuana and oral cannabinoids (Mendelson and Mello 1984; Chait and Zacny 1992), whereas other studies have reported that smoked marijuana produces a

greater high and larger increase in heart rate than oral THC (Lemberger et al. 1972; Cocchetto et al. 1981; Hollister et al. 1981; Ohlsson et al. 1981; Agurell et al. 1984). It is difficult to rule out pharmacokinetic factors in these comparisons. Several studies (described in Iverson 2000) have compared the antiemetic effects of oral THC to smoked THC in patients receiving chemotherapy, with no clear advantage for the smoked form. However, the clinical assessments of efficacy are also complicated by the psychoactive effects of the drug, which are unpleasant to many patients.

Despite the many similarities in the effects of THC and whole plant marijuana in the present studies, small differences were evident in both experiments. In the oral study, subjects reported feeling a greater drug effect (DEQ) in the THCHigh compared to the MjHigh condition, and the THCHigh condition resulted in greater increases on the ARCI A (stimulant) and LSD (sensory/dysphoria) scales than the MjHigh condition. However, these differences may have been due to the higher plasma levels of THC attained in the THCHigh condition than the MjHigh condition. On the other hand, the equivalence of subjects' responses on other measures of subjective effects between the THCHigh and MjHigh conditions (e.g. ARCI Marijuana scale and DEQ "high"), despite differences in plasma levels, may suggest that other cannabinoids in the marijuana augmented these responses. It is difficult to determine whether these differences across variables are due to measurement error or whether they reflect true pharmacological differences.

In the smoking study, there were small differences between the effects of THC and marijuana with equivalent plasma concentrations. Marijuana induced a greater increase in heart rate, greater subjective effects on the ARCI, and more pronounced reports of feeling a drug effect than THC-only, especially at the lower dose. Although the differences between THC-only and whole-plant marijuana were small, they suggest that other cannabinoids in the marijuana plant may have contributed to the effects. For example, cannabinol (at a concentration of 0.30%) was one constituent of the marijuana used in these studies. Although cannabinol does not have THC-like effects itself (Hollister 1973; Perez-Reyes et al. 1973), it has been shown to enhance subjects' reports of feeling drugged, drunk, dizzy, and drowsy in response to THC (Karniol et al. 1975; Musty et al. 1976). Thus, it would be of interest systematically to vary the concentrations of cannabinol and other cannabinoids to determine whether they contribute to the effects of marijuana. Although the concentrations of cannabinoids in the present experiment were within the range detected in marijuana samples confiscated in the United States between 1980 and 1997 (ElSohly et al. 2000), there is a wide range of variability in confiscated samples (e.g. cannabinol varied from 0.18 to 0.57%, and cannabidiol varied from 0.01 to 0.61). Thus, it is possible that marijuana samples with higher levels, or different ratios of these constituents may produce other effects.

Several factors limit the conclusions that can be drawn from these findings. First, THC and marijuana effects in the smoking study were not clearly dose-dependent, raising some question about the sensitivity of the procedure to detect subtle differences between the drugs. The lack of dose-dependency may have been due to the artificial smoking procedure used in our laboratory study. However, other studies that involved smoking in a more customary fashion also failed to detect dose-dependent subjective response to marijuana (Perez-Reyes et al. 1982). Second, the conclusions are limited to the particular subjective and behavioral effects that were measured. It is possible that other dependent measures, such as neuropsychological measures or measures that are more relevant to therapeutic effects (such as analgesia or muscle relaxant effects) would reveal differences between THC and marijuana. Third, metabolites of THC such as 11-OH-THC were not measured, leaving open the possibility that differences in metabolites between the marijuana and THC conditions contributed to the results. Finally, the conditions under which these drugs are administered in the laboratory may differ from the conditions under which marijuana is used in the non-laboratory setting. For example, in the smoking study the rate, depth or frequency of smoking may have affected the outcome, and in the oral study other dietary constituents or the manner of preparing the material may have affected responses to the drug.

In summary, the present results suggest that THC accounts for most of the subjective effects of marijuana, and lend little support to the idea that other cannabinoids contribute significantly to psychoactive effects of marijuana. Nevertheless, it is still possible that specific cannabinoids found in the marijuana plant contribute to the other behavioral or physiological effects of the drug, including their potential therapeutic effects. Future studies involving systematic variation of the concentrations and ratios of selected cannabinoids, and using a range of outcome measures, are needed to resolve these questions.

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