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Responses to Oral Δ^9-Tetrahydrocannabinol in Frequent and Infrequent Marijuana Users

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KIRK, J. M. AND H. DE WIT. *Responses to oral Δ^9-tetrahydrocannabinol in frequent and infrequent marijuana users*. PHARMACOL BIOCHEM BEHAV. **63**(1) 137–142, 1999.—It is known that an individual's drug use history affects the quality of subjective effects experienced following administration of several clinically used psychoactive drugs such as barbiturates, diazepam, and morphine. However, it is not known whether drug use history also affects responses to therapeutic cannabinoids such as Δ^9-THC. The current experiment compared the subjective and behavioral effects of oral Δ^9-THC in two groups of volunteers: frequent users (FREQ; $n = 11$), who reported using marijuana at least 100 times, and infrequent users (INF; $n = 10$) who reported using marijuana 10 or fewer times. Subjects participated in three sessions during which they received Δ^9-THC (7.5 and 15 mg) and placebo. They completed subjective effects questionnaires for 5 h following administration. In the FREQ group, the lower dose (7.5 mg) increased ratings of "feel drug," relative to placebo, whereas it had no effect in the INF group. In contrast, at the higher dose (15 mg), ratings of "feel drug" were lower in the FREQ group than in the INF group, suggestive of tolerance. In addition, the INF group reported greater sedative effects than the FREQ group following the higher dose of Δ^9-THC, again suggesting tolerance to Δ^9-THC's sedative effects. These findings demonstrate that marijuana use history may affect the subjective effects of oral Δ^9-THC, but that the influence of drug use history depends on the dose of drug administered. These findings may have implications for the clinical use of Δ^9-THC and other cannabinoids.

Oral Δ^9-THC Marijuana Drug use history Subjective effects

Δ^9-THC is the principal active constituent of the marijuana plant (*Cannabis sativa*). Clinical trials have shown this drug to be an effective antiemetic when used by patients receiving cancer chemotherapy (15,17,24). More recent clinical trials have shown Δ^9-THC to be an effective appetite stimulant in patients suffering from cancer or AIDS cachexia (3,23). Further, anecdotal evidence suggests that the compound may be useful for a wide variety of other therapeutic uses. However, the therapeutic utility of Δ^9-THC may be limited because of the negative psychoactive effects (e.g., dysphoria and confusion) it produces in some individuals (15,23). Understanding what factors affect an individual's responses to oral Δ^9-THC may help to select the most appropriate doses to be used in different individuals.

One factor that has been shown to affect the quality of subjective effects that a person may experience from a psychoactive drug in a clinical setting is the patient's history of psychoactive drug use. It is well documented that subjects with histories of habitual psychoactive drug use generally report greater euphoric and less dysphoric effects when administered psychoactive drugs such as benzodizepines, barbiturates, and morphine in a clinical or laboratory setting (2,5,8,10,11,16). Several studies have investigated the effects of marijuana use history on subjective responses to drugs. Results from these studies have been mixed. In some studies it has been found that regular marijuana users report greater euphoric effects from drugs such as nitrous oxide and marijuana than nonusers, while in other studies the reverse effect or no differences between users and nonusers have been reported (4,12,18–21,26). Differences in methodologies, including lack of blinded drug administration, no placebo, differences in experimental setting, and range of doses used, may help to explain the discrepant findings. To date, no study has evaluated effects of marijuana use history on responses to oral Δ^9-THC.

The current experiment investigated the influence of a history of marijuana use on subjective responses to moderate doses of oral Δ^9-THC, in a controlled laboratory setting and using standardized drug effects questionnaires. Two groups of subjects were used: one group consisted of subjects who reported regular use of marijuana, and the other group con-

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sisted of subjects who had used this drug less than 10 times in their lives. Based on previous research, it was hypothesized that subjects with extensive marijuana use histories would report greater pleasant effects from oral Δ^9-THC than those without such histories.

METHOD

Subjects

Twenty-one healthy males (n = 12) and females (n = 9) participated. Eleven of these subjects were frequent marijuana users (FREQ group) who reported use of marijuana on at least 100 occasions in their lifetime, use for at least 1 year, and current use of marijuana at least twice per month. Ten subjects were infrequent users of marijuana (INF group) who reported using marijuana on 10 or fewer times in their lifetime and no use of marijuana within the past 4 years. Candidates were given a psychiatric interview (DSM-IV; 1) to ensure that they did not have a current or previous psychiatric disorder, including Substance Abuse and Dependence, and they completed a symptom checklist, the SCL-90 (6), to rule out those with current serious psychiatric symptomatology. Additionally, candidates were given an electrocardiogram and were examined by a physician to ensure that they were physically healthy.

Prior to participation, subjects provided informed consent. Subjects were told that the purpose of the experiment was to investigate effects of drugs on mood and behavior. They were told that they might receive a stimulant, sedative, antihistamine, antidepressant, antiemetic, or placebo. The consent form also listed the possible side effects of each of these drugs. Subjects were asked not to smoke tobacco for 6 h prior to any session, and not to take any recreational drugs 24 h prior to or following sessions. The study was approved by the local institutional review board, and subjects were paid for their participation.

Design and Procedure

Before the study began, subjects participated in a 1-h orientation session to familiarize them with the dependent measures. Then, subjects participated in three evening sessions (1730–2300 h) conducted once per week. The evening time was selected to correspond with the time of day when most individuals use marijuana and other drugs recreationally. On the three sessions, subjects received a capsule that contained placebo or one dose (7.5 or 15 mg) of Δ^9-tetrahydrocannabinol (Δ^9-THC; Marinol^R: Roxane, Inc.) administered double blind. Δ^9-THC was placed in size 00 hard gelatin capsules and filled with dextrose. Placebo capsules contained only dextrose. Subjects received one dose per session, and the order of presentation of doses was counterbalanced across subjects.

Subjects were tested in testing groups of two to four, each testing group consisting of individuals from the same experimental group (FREQs or INFs). Sessions were conducted in a laboratory designed to resemble a comfortable living room. The room contained sofas, tables, television, videocassette recorder, radio, and a selection of games and movies. Subjects were allowed to engage in recreational activities such as playing games or watching television or movies, except during times when they completed questionnaires or had their heart rate measured. Subjects were not allowed to work or study during sessions.

Subjects arrived at the laboratory at 1730 h and provided a baseline breath alcohol sample to verify that they were ethanol free. Breath alcohol level was determined using an Alco-Sensor III hand-held breath test (Intoximeters, Inc.: St. Louis, MO). At 1800 h, baseline measures were obtained, including the subjective effects measures (ARCI and VAS, see below), a psychomotor task (DSST, see below) and heart rate. Then subjects ingested a capsule containing 7.5 or 15 mg Δ^9-THC or placebo (dextrose only) with 100 ml water. Drug administration was double blind, and different subjects within each group tested together received different orders. Every 30 min after taking the capsule until 2200 h, and then again at 2300 h, subjects completed additional subjective effects questionnaires (ARCI, DEQ, and VAS), performed the psychomotor task (DSST), and their heart rate was measured. A snack was provided at 2000 h after the dependent measures at this time were completed. At 2300 h, after other measures had been completed, subjects completed an end-of-session questionnaire (see below) and were transported home. Upon completing all three experimental sessions, a debriefing session was conducted with each subject to explain the study and pay the subjects.

Dependent Measures

Four measures of subjective drug effects were obtained:

1. Addiction Research Center inventory. A 53-item version of the Addiction Research Center Inventory [ARCI; (9)] was used. It was comprised of six empirically derived scales that are sensitive to various classes of drug effects, including the Marijuana (M) scale, which measures marijuana-like effects, the Amphetamine (A) and Benzedrine-Group (BG) scales, which measure stimulant-like effects, the Lysergic acid (LSD) scale, which measures dysphoria and somatic effects, the Morphine-Benzedrine scale (MBG), which measures euphoria, and the Pentobarbital-Chlorpromazine-Alcohol scale (PCAG), a measure of sedation.
2. Visual analog scales. Four visual analog scales (VAS) were administered, on which subjects indicated the extent to which they were feeling "stimulated," "anxious," "sedated," and "hungry." The left ends of the scales were labeled "not at all" and the right ends were labeled "very."
3. Drug effects questionnaire. The Drug Effects Questionnaire (DEQ) contained four 100-mm visual analog scales. These scales consisted of ratings of "feel" effects, "like" effects, "high," and "want more." The scales for "feel," "high," and "want more" were labeled "not at all" on the left end and "a lot" at the right end (or "very much" for ratings of "want more"). The "like" effects scale was labeled "dislike a lot" at the left end, "neutral" at the 50 mm point, and "like a lot" at the right end.
4. End-of-session questionnaire. The End-of-Session Questionnaire (EOS) consisted of four questions regarding subjects' overall subjective experiences during the session. On the first question, subjects rated on a five-point scale the overall effects they experienced from the drug, from 1 ("I felt no effect at all") to 5 ("I felt a very strong effect"). Next, on a 100-mm line, they rated the extent to which they liked or disliked the effects of the drug, from "disliked a lot" to "liked a lot" (50 indicated "neutral"). Then they selected from a list of six possible drugs (those listed on the consent form) what drug they thought they received, and on the last question, they responded "yes" or "no" to the question "If you had the opportunity to take this drug again, would you?"

TABLE 1
DEMOGRAPHIC CHARACTERISTICS AND DRUG USE HISTORY OF PARTICIPANTS

	FREQs	INFs
n	11	10
Mean age (SD)	27.6 (5.18)	25.1 (3.57)
Gender (male/female)	7/4	5/5
Current drug use (last 30 days)		
Alcohol: % subjects use	100	100
Mean drinks/week	6.9	3.1
Tobacco: % Subject use	60	10
Users: mean cigarettes/day	6	8
Caffeinated Coffee: % subject use	80	60
Users: mean cups/week	5.7	15
Marijuana: mean joints/week	3.5	0
Lifetime drug use (*n*; never/< 10/10–50/50 + times)		
Marijuana	0/0/0/11	5/4/1/0
Stimulants	5/4/1/1	7/3/0/0
Tranquilizers	8/3/0/0	8/2/0/0
Hallucinogens	4/4/2/1	10/0/0/0
Opiates	9/2/0/0	10/0/0/0
Other drugs	8/2/1/1	10/0/0/0

Digit Symbol Substitution Test. The Digit Symbol Substitution Test [DSST; (25)] of the Wechsler Adult Intelligence Scale is a time-based paper-and-pencil test of psychomotor ability. At the top of the form, a legend showed the numbers 1–9 and their corresponding symbol. The remainder of the page contained several rows of numbers under which subjects were instructed to draw the corresponding symbol. The number of correct responses made in 60 s was recorded.

Heart rate. Resting heart rate was measured using a digital, battery-operated blood pressure and heart rate monitor.

TABLE 2
SUMMARY OF SIGNIFICANT *F*-VALUES (ANOVA) FOR EACH DEPENDENT MEASURE

Measure	D	H	D × H	D × G	D × H × G
ARCI					
A	3.41	1.93			
BG	3.26	11.29**	4.85**	4.74*	1.66
MBG		2.64			
LSD	33.19**	9.30**		5.11**	
M	30.88**	16.21**	4.07**	5.16*	
PCAG	8.60**	12.01**	5.54**	6.21**	1.93*
DEQ					
Feel	47.47**	29.41**	9.84**	5.30*	3.14**
Like		2.30	2.11*	4.26	
High	26.21**	17.46**	6.44**		1.72
Want More		4.64**			
VAS					
Stimulated	15.91**	10.49**	5.19**		
Sedated	19.47**	7.52**	2.74**		
Anxious	7.94*	3.56**	3.64**		
Hungry	7.60**				
DSST		2.05	1.88		1.74
Heart Rate	10.39**	2.42*			
End of session (no H factor)					
Feel	30.5**	—	—	4.36*	—
Like:		—	—	10.05**	—

Factors are drug (D; THC 7.5 or 15 mg vs. placebo), hour (H), and group (G; FREQ vs. INF). No value indicates no significant effect, a value with no asterisks indicates $p < 0.05$, one asterisk (*) indicates $p < 0.01$, and two asterisks (**) indicate $p < 0.001$. There were no significant main effects of group (G) and no G×H interactions.

Data Analysis

Subjective measures, psychomotor performance, and heart rate were analyzed using separate 2 × 3 × 10 (group × dose × hour) mixed-factor analyses of variance (ANOVAs) for each dependent measure. The criterion for statistical significance was set at $p < 0.05$.

RESULTS

Demographic characteristics and current and lifetime drug use histories of two subject groups are reported in Table 1. In addition to using marijuana, subjects in the FREQ group were also more likely than subjects in the INF group to report having used other recreational drugs, including alcohol and nicotine. Table 2 summarizes the *F*-values for all significant effects on the subjective and behavioral measures.

Overall Effects of Δ⁹-THC

Δ⁹-THC produced several prototypic cannabinoid-like drug effects. First, it increased heart rate, a physiological index of cannabinoid effects. The peak increase over baseline was 6.7 bpm for the 7.5 mg dose and 6.4 bpm for the 15 mg dose (Fig. 3). THC also produced robust dose-dependent increases in ratings on the ARCI LSD scale, a measure of somatic effects, and on VAS measures of stimulation and sedation. On all three of these scales the effects peaked between 2.5–3.5 h after drug administration, and approached baseline levels by the end of the session. Other significant, but modest, effects of Δ⁹-THC included dose-dependent increases on ARCI MBG (Euphoria) ratings, VAS ratings of anxious, and decreases in DSST performance.

Effects of Drug Use History

The FREQ and INF groups responded differently to the Δ⁹-THC on several measures of subjective drug effects, but the differences depended on the dose administered. The 7.5 mg dose of Δ⁹-THC increased ratings of "feel" effects, "high" (DEQ), and ARCI Marijuana scale scores in the FREQ group, but not the INF group. At the higher dose the drug increased these measures in both groups (Figs. 1 and 2). On other measures, however, the 15-mg dose produced greater effects in INF group compared to the FREQ group (Figs. 1 and 2). At this dose, subjects in the INF group reported significantly more sedative-like effects, as measured by the ARCI PCAG scale, than subjects in the FREQ group. Consistent with this finding, the INF subjects also reported a decrease in stimulant-like effects [ARCI Benzedrine (BG) scale], which was not observed in the FREQ subjects. There was also a nonsignificant trend for INFs to report greater sedation and less stimulation than FREQs on the VAS. Finally, at the 15-mg dose of THC the INFs reported significant and substantial decreases in VAS ratings of "like" effects, whereas liking ratings in the FREQ's did not differ from placebo. This effect was also apparent on the end-of-session ratings of liking: liking ratings at the end of the session after the 15-mg dose were 27.3 (SEM 7.9) in the INF group, and 57.9 (SEM 7.4) in the FREQ group (significant drug by group interaction; Table 2). The groups did not differ in their responses to Δ⁹-THC on measures of heart rate, psychomotor performance, or other subjective effects. They also did not differ in their responses to the end-of-session question regarding whether they would take the drug again (most would not) or what they thought they had received.

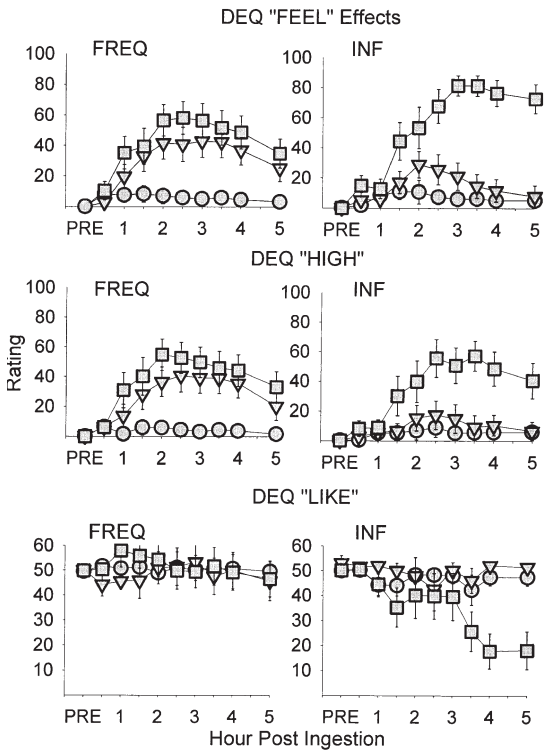

FIG. 1. Mean (SEM) ratings for DEQ "feel effects," "high," and "like," shown for each of the three experimental conditions [placebo (circles), 7.5 mg Δ⁹-THC (triangle) and 15 mg Δ⁹-THC (squares)]. Frequent users (FREQ; $n = 11$) are shown in the left panels and infrequent users (INF; $n = 10$) are shown in the right panels.

DISCUSSION

The current experiment demonstrated that individuals with a history of frequent marijuana use exhibit different subjective responses to oral Δ⁹-THC than individuals without such a history, but that the quality and magnitude of these differences depend on the dose of Δ⁹-THC administered. At the lower dose, Δ⁹-THC was more clearly detected as a drug effect in the frequent users compared to the infrequent users. For example, subjects in the FREQ group exhibited greater increases in ratings of "feel drug" and "high," and higher scores on the ARCI M scale after 7.5 mg Δ⁹-THC, compared to subjects in the INF group. However, these effects were specific to certain subjective ratings of drug effect: No differences were observed in the physiological or psychomotor responses to this dose. In marked contrast, at the higher dose, FREQ's reported lesser effects on certain measures than the INF group: 15 mg Δ⁹-THC produced less sedation in the FREQ group than in the INF group, and the INF group reported greater dislike of the drug's effect than the FREQs. These differences at the higher dose of THC are consistent with the notion that the FREQs were more tolerant to these effects. Irrespective of drug use history, Δ⁹-THC produced several prototypic effects, including dose-dependent increases in heart rate, stimulant- and sedative-like effects, increases on the ARCI Marijuana scale, and dose-dependent decreases in DSST performance. These findings are consistent with those observed in other studies using similar doses of Δ⁹-THC and experienced marijuana users [e.g., (14)].

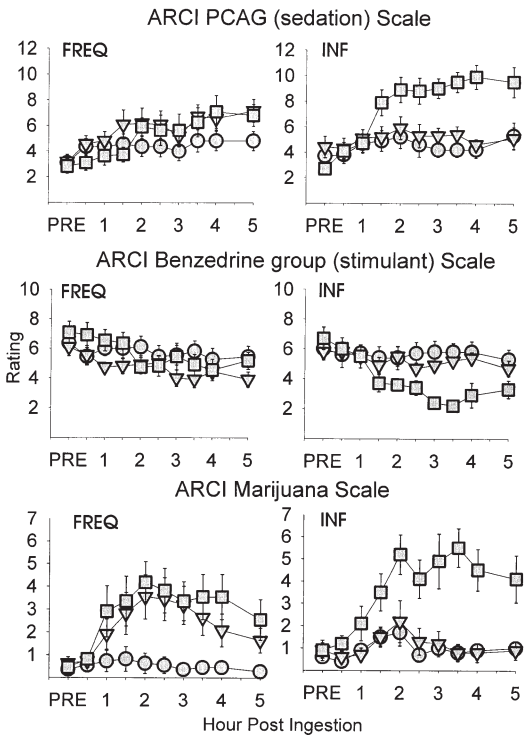

FIG. 2. Mean (SEM) ratings for ARCI sedation (PCAG), stimulant (BG), and marijuana (M) scales, shown for each of the three experimental conditions [placebo (circles), 7.5 mg Δ^9-THC (triangles) and 15 mg Δ^9-THC (squares)]. Frequent users (FREQ; $n = 11$) are shown in the left panels and infrequent users (INF; $n = 10$) are shown in the right panels.

There are several explanations as to why individuals with histories of drug use would report greater sensitivity than INFs to the lower dose of THC. First, conditioning and expectancies may play an important role in detecting and reporting effects. Even though subjects were blind to the drug that was administered, the effects of Δ^9-THC are similar to the effects of marijuana, and individuals with extensive experience with marijuana may be better able to identify the subtle effects of the low dose of Δ^9-THC as a drug effect. These subjects may even have recognized the effects as marijuana-like, and these cognitions may, in turn, have influenced their responses. It has been shown that the belief that a certain drug has been ingested can influence subjects' ratings of drug liking and reports of euphoria (14). An alternative explanation for these findings is that repeated exposure to marijuana may have produced sensitization to the effects of Δ^9-THC in the FREQs. However, the two groups did not differ on physiological measures (heart rate) or psychomotor performance after THC, suggesting that this sensitization at least did not occur at the receptor level. Although it is possible that sensitization developed to one measure (e.g., subjective effects) and not another (e.g., heart rate), this is not the most parsimonious explanation of the results. Moreover, sensitization to the effects of marijuana has not been reported to occur in laboratory animals. It seems more likely that the group differences at the low dose were related to the ability to identify and label the subtle subjective changes as drug effects.

At the higher dose the FREQ and INF groups also differed in their responses to Δ^9-THC, but the group differences were quite unlike, and in some cases directly opposite, to the differences observed at the lower dose. Subjects in the INF group reported greater effects from the drug than subjects in the FREQ group on ratings on DEQ "Feel" effects. Subjects in the INF group also reported more sedative-like effects following the high dose of Δ^9-THC than did FREQs. Both of these effects are consistent with the idea that the subjects in the FREQ group were tolerant to the effects of Δ^9-THC because of their regular marijuana use. Surprisingly, however, the groups did not differ in their sensitivity to the effects of 15 mg Δ^9-THC on measures of physiological effects or psychomotor impairment, suggesting that the subjective effects measures may be more sensitive indices of the effects of low doses of psychoactive drugs than physiological or performance measures. Alternatively, it may be that tolerance develops differentially to these subjective vs. physiological effects. Tolerance to the behavioral and physiological effects of Δ^9-THC has been well documented in laboratory animals (7), but it has been surprisingly difficult to demonstrate in humans (13,22). This may be due to the relatively low doses typically used in humans compared to laboratory animals, or it may be related to the type of dependent measures typically examined in human studies, compared to animal studies. It is notable that even among the measures obtained in the present study, the FREQ group appeared to be tolerant to some of the subjective effects (e.g., sedative-like subjective effects), but not to others (e.g., "high"). The factors that influence the magnitude of subjective and behavioral responses to Δ^9-THC clearly require additional research.

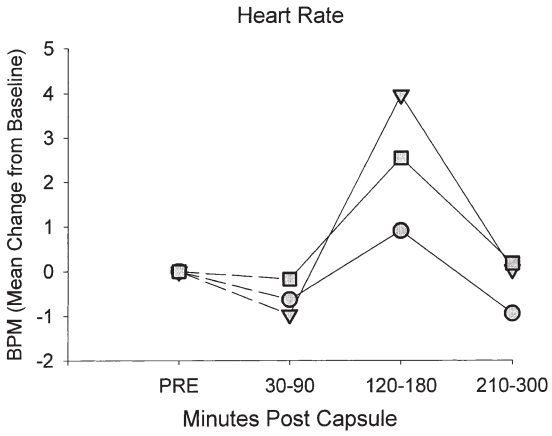

FIG. 3. Mean heart rate after placebo (circles), 7.5 mg Δ^9-THC (triangles) and 15 mg Δ^9-THC (squares), for all 21 subjects. The frequent users and infrequent users did not differ on this measure.

The results of the current experiment show that marijuana use history can influence responses to oral Δ^9-THC, but that it depends on the dose of Δ^9-THC. These findings have implications for both laboratory research and clinical practice. In behavioral pharmacology studies with humans, the findings show that it is important to control for subjects' histories of drug use, as this may account for some individual differences in responses to cannabinoids and possibly other drugs. It also underscores the importance of determining the effects of a drug across a range of doses: for example, it cannot be assumed that group differences observed at one dose reflect a shift in the entire dose–response function. In fact, the markedly different effects observed in the two groups after the two doses of Δ^9-THC suggest that more than one process mediated the group differences at the two doses. With regard to implications for clinical practice, these findings suggest that

patients without experience with marijuana may experience greater sedation from relatively high therapeutic doses of Δ^9-THC than patients who are experienced marijuana users. It is notable, however, that no differences were observed on the increase in heart rate, indicating that the drug is not necessarily less safe in the inexperienced users. The current research leaves many questions unanswered. Future research is needed to further investigate the interactions between drug use history, expectancies, and pharmacological responses to drugs across different dependent measures. These factors are likely to account for some of the individual differences in responses to Δ^9-THC and other cannabinoids.

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