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Effects of Expectancies on Subjective Responses to Oral Δ^9-Tetrahydrocannabinol

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KIRK, J. M., P. DOTY AND H. DE WIT. *Effects of expectancies on subjective responses to oral Δ^9-tetrahydrocannabinol.* PHARMACOL BIOCHEM BEHAV **59**(2) 287–293, 1998.—The effects of expectancies on subjective responses to oral Δ^9-tetrahydrocannabinol (Δ^9-THC) were examined. Thirty-five regular marijuana users were assigned to one of two groups: one group was told that they may receive a cannabinoid or placebo and a second group was told that they may receive a drug from one of several classes of drugs (e.g., stimulant, sedative, antiemetic) or placebo. Regardless of the group to which they were assigned, subjects received each of two oral doses of Δ^9-THC (7.5 and 15 mg) and placebo, one dose per session, for a total of three sessions. Measures of subjective effects, including visual analog scales and the Addiction Research Center Inventory (ARCI), were administered at 0.5-h intervals throughout each session. Consistent with previous research using other drugs, subjects in the current experiment who expected to receive a cannabinoid reported greater pleasurable effects than subjects who did not have this expectancy. The results have implications for understanding the effects of cannabinoids when used in both recreational and clinical settings. ©1998 Elsevier Science Inc.

Δ^9-THC Cannabinoids Expectancies Marijuana users Subjective drug effects

IT is well documented that, in human self-administration experiments, information given to subjects about the identity of a drug can influence both their subjective and behavioral responses to that drug. These expectancy effects have been extensively demonstrated with ethanol [e.g., (10)]. Recently, expectancy effects have been observed in studies using caffeine (8,13) and amphetamine (12). In these recent experiments, subjects who were provided with information about the drug's identity reported greater pleasurable effects from the drug.

To date, the influence of expectancies on subjective effects of cannabinoids has not been explored. A possible reason for this omission is that it is difficult to blind subjects to the identity of smoked marijuana, therefore making expectancies difficult to control. Oral Δ^9-tetrahydrocannabinol (Δ^9-THC), the principal psychoactive constituent of the marijuana plant, has been shown to produce a profile of subjective effects similar to that of whole plant marijuana (3). Hence, oral Δ^9-THC is a convenient drug to use to examine the role of expectancies in the subjective effects of cannabinoids. In previous research with oral Δ^9-THC, subjects have always been informed that they may receive a cannabinoid [e.g., (3,4,11). Thus, in these experiments, it is impossible to separate the pharmacological effects from the expectancies.

The current study examined the influence of expectancies on subjective responses to oral Δ^9-THC by manipulating the information subjects were given about the drug's identity. Two groups of experienced marijuana users were used: one group was told that they would receive a cannabinoid or placebo, and a second group was told that they would receive a drug from one of several classes of drugs (e.g., stimulant, antidepressant, or antiemetic). It was predicted that subjects who expected to receive a cannabinoid would report greater euphoric effects compared to subjects who were not provided with this information.

METHOD

Subjects

Thirty-five healthy male (n = 19) and female (n = 16) volunteers [mean age (SD) = 23.5(4.3)] participated. The majority of subjects were Caucasian, single, undergraduate college students who were of normal weight. Table 1 summarizes the

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TABLE 1
SUBJECT DEMOGRAPHICS AND DRUG USE HISTORY

	INF	NON
n		
Mean Age	18	17
Gender (male/female)	24	23
Mean weight (lb)	9/9	10/7
Current drug use (last 30 days)[a]	144	144
Alcohol		
% Subject use	100	100
Mean drinks/week	4.6	6
Tobacco		
% Subject use	44.4	64.7
Mean cigarettes/week	42	86
Caffeinated Coffee		
% Subject use	100	94.1
Mean cups/wk	11.4	13.3
Lifetime drug use (<10/10–50/50+times)[b]		
Marijuana	0/8/10	0/5/12
Stimulants	4/1/1	5/2/1
Tranquilizers	2/0/0	5/1/0
Hallucinogens	11/4/0	8/4/0
Opiates	8/2/0	7/6/0

[a]Means reflect data from users only.
[b]Number of subjects reporting use.

demographics and drug use histories of both subject groups. To be included in the experiment, subjects had to report (a) use of marijuana for at least 1 year, (b) use of marijuana at least 10 times in their lifetime, and (c) use of marijuana within the past 2 months. Candidates were given a psychiatric interview [DSM-IV; (1)] to ensure that they did not have a current or previous psychiatric disorder, and they completed the SCL-90 (6). Additionally, candidates were given an EKG 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. The consent form listed the classes of drugs subjects may be given, including stimulant, sedative, antihistamine, antidepressant, or placebo and, depending on the group, cannabinoid or antiemetic (see Design below). The consent form also listed an extensive list of possible side effects 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

Subjects were randomly assigned to one of two instructional groups. For subjects in Group Informed (INF), "cannabinoid" was included as an option on the consent form. Prior to participation, subjects in this group were told by the experimenter that they would receive a cannabinoid or placebo. These subjects were also told that cannabinoids are drugs found in the marijuana plant. For subjects in Group Noninformed (NON), "antiemetic" was listed as an option on the consent form, and these subjects were not given any additional information about what drug they would receive.

Subjects participated in three sessions conducted once per week. On these three sessions, subjects received capsules containing Δ^9-THC in sesame oil (Marinol®: UNIMED, Inc.; 7.5 and 15 mg) and placebo, administered double blind. The drug was placed in a size 00 gelatin capsule and filled to capacity with dextrose. Placebo capsules contained only dextrose. Sub-

TABLE 2
SIGNIFICANT F-VALUES FOR MAIN EFFECTS AND INTERACTIONS

	D	H	G	D×H	D×G	H×G	D×H×G
Measure	*F*(2, 66)	*F*(9, 297)	*F*(1, 33)	*F*(18, 594)	*F*(2, 66)	*F*(9, 297)	*F*(18, 594)
DEQ							
Feel	47.06†	19.67†		7.74†			
Like	3.08‡	8.07†				2.40*	
High	45.54†	17.28†		6.12†			
More	7.95†	9.94†	4.28*	3.44†			
VAS							
Stimulated	11.19†	13.28†		4.77†			
Sedated	12.16†	6.08†					
Anxious	5.69**	2.88*		2.19*			
Hungry	3.31*	34.50†		2.86**			
ARCI							
A		3.64**					
BG	8.52†	11.14†		2.56**			
MBG		4.43†	4.91*				
LSD	14.48†	11.56†		4.54†			
M	21.57†	15.88†		7.67†			
PCAG	11.44†	14.21†		5.05†			
Heart rate	10.79†	11.97†		4.65†			2.19‡
DSST				1.92*			

"D," "H," and "G" represent dose, hour, and group, respectively.
*$p < 0.05$, ** $p \leq 0.01$, †$p \leq 0.001$, ‡$p = 0.06$.

jects received one dose per session and the order of presentation of doses was counterbalanced across subjects.

Dependent Measures

Blood alcohol level. Presession blood alcohol level was estimated by breath alcohol level (BAL) as determined using an Alco-Sensor III hand-held breath test (Intoximeters, Inc.: St. Louis, MO).

Drug effects questionnaire. The Drug Effects Questionnaire (DEQ) contained four visual analog scales 100-mm in length. The scales consisted of ratings of "feel" effects, "like" effects, "high," and "want more." The left ends of these scales were labeled "not at all" (or "dislike a lot" for ratings of "like" effects). The right ends of these scales were labeled "a lot" for the first three scales and "very much" for the last scale.

Visual analog scales. On four other visual analog scales (VAS) subjects were asked to report 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."

Addiction Research Center inventory. A 53-item version of the Addiction Research Center Inventory [ARCI; (9)] was employed in the current experiment. This version of the ARCI consists of six empirically derived subscales that are sensitive to various classes of drug effects: the Morphine-Benzedrine scale (MBG) is a measure of euphoria, the Pentobarbital-Chlorpromazine-Alcohol scale (PCAG) is a measure of sedation, the Amphetamine (A) and Benzedrine-Group (BG) scales are measures of stimulant-like effects, the Lysergic acid (LSD) scale is a measure of dysphoria and somatic effects, and the Marijuana (M) scale is sensitive to marijuana effects.

Digit Symbol Substitution Test. The Digit Symbol Substitution Test [DSST; (14)] of the Wechsler Adult Intelligence Test is a time-based paper-and-pencil test on which subjects are asked to transpose numbers and their associated symbols as quickly and accurately as possible. The number of correct responses made in 60 s is recorded.

End-of-Session Questionnaire. The End-of-Session Questionnaire (EOS) contained four questions regarding subject's experiences with the capsule they ingested. (a) Subjects were asked to rate the overall effects of the capsule on a five-point scale. A "1" represented "I felt no effect at all," and a "5" represented "I felt a very strong effect." (b) Subjects rated on a 100-mm line whether or not they liked or disliked the effects of the capsule. The left end was labeled "dislike a lot" and the right end was labeled "like a lot." (c) Subjects selected from a list what drug they thought they received. Subjects in the NON group were given a choice between one of the five classes of drugs listed on the consent form and placebo. Subjects in the INF group were given a choice between cannabinoid and placebo. (d) Subjects answered a yes/no question regarding whether or not they would take the drug again.

Session Procedure

Before the first session, subjects participated in a 1-h orientation session to familiarize them with the dependent measures followed by three 5.5-h experimental sessions held in

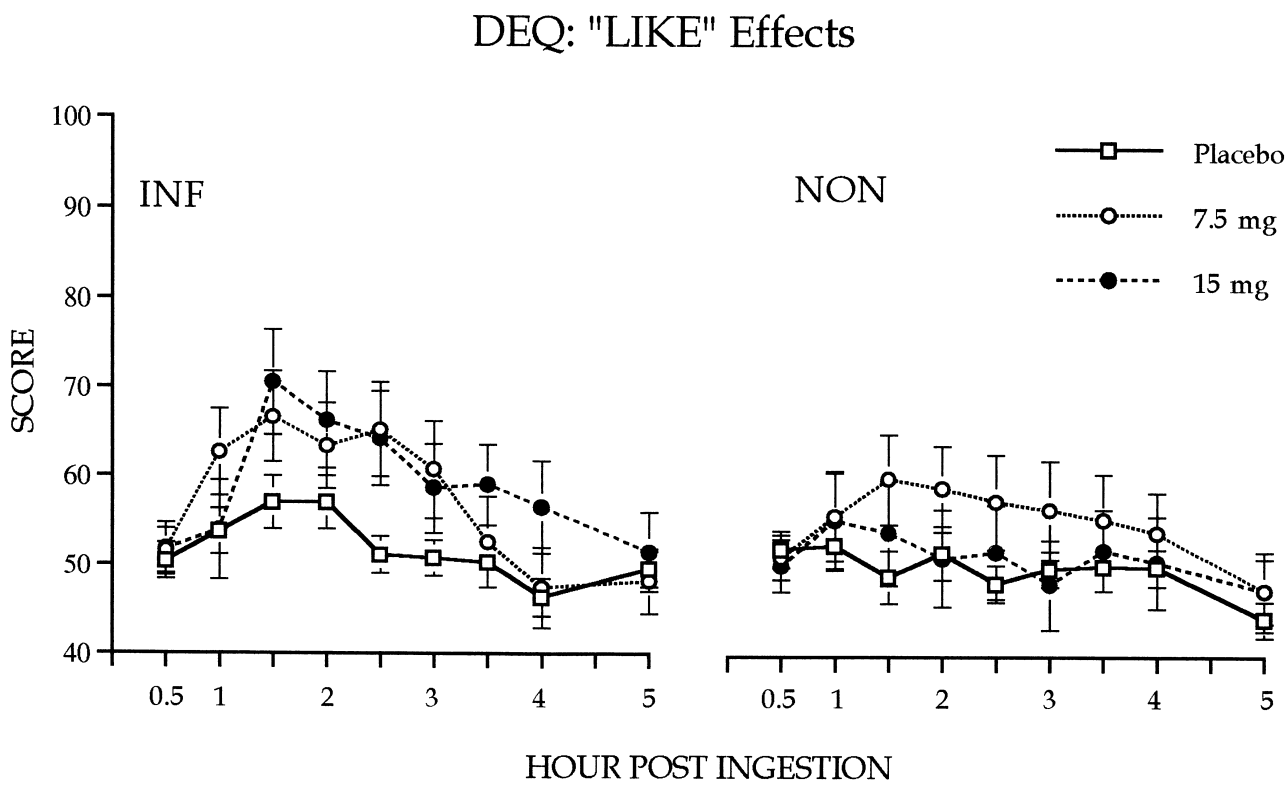

FIG. 1. Group means and standard errors for DEQ ratings of "like" effects, shown for each hour and for each session. The left panel shown means for group INF and the right panel shows means for group NON. A rating of 50 indicates "neutral." Ratings above and below 50 represent greater liking and disliking, respectively.

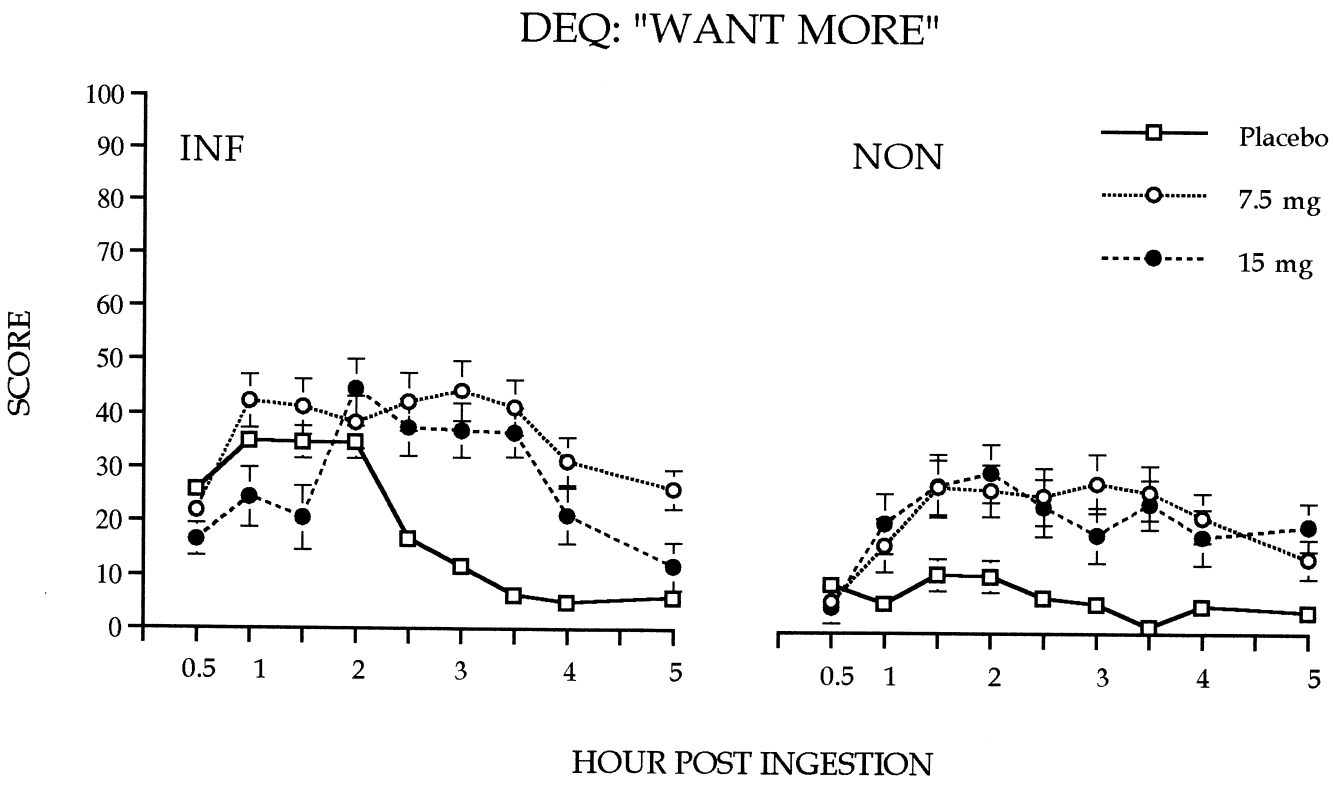

FIG. 2. Group means and standard errors for DEQ ratings of "want more" drug, shown for each hour and for each session. The left panel shows means for group INF and the right panel shows means group NON.

the evening. Sessions were conducted using two to four members of the same subject group (i.e., informed and noninformed subjects did not participate together).

The sessions took place in a laboratory designed to resemble a comfortable living room. The room contained sofas, tables, a television, a VCR, a radio, and a selection of games and movies. When no dependent measures were being taken, subjects were allowed to engage in recreational activities such as playing games or watching television or movies. Subjects were not allowed to work or study.

Subjects arrived at the laboratory at 1730 h and provided a baseline BAL to verify that they had not been drinking prior to the session. At 1755 h heart rate was measured and subjects completed baseline measures including the VAS, ARCI, and DSST. At 1800 h subjects ingested a capsule that contained either active drug or placebo with 100 ml water. Beginning at 1830 h, heart rate was measured and the DEQ, VAS, ARCI, and DSST were administered at 0.5-h intervals until 2200 h and then again at 2300 h. Additionally, at 2300 h, subjects completed the EOS and were transported home. Subjects were given a snack at 2000 h after the dependent measures at these times were completed.

RESULTS

Dependent measures were analyzed using separate three-way (dose × hour × group) mixed-factor analyses of variance (ANOVAs). For tests of within-subjects effects, Huynh-Feldt corrections were used to protect against violations of sphericity. The criterion for statistical significance was set at $p < 0.05$. Table 2 shows significant main effects and interactions for all dependent measures.

DEQ

Both drug and information (group) affected subjects' responses on scales of the DEQ. The groups responded differently on ratings of "like" effects (significant hour × group interaction) and "want more" (significant main effect of group). Group INF, compared with group NON, reported higher ratings of "like" effects (see Fig. 1) and "want more" drug (see Fig. 2) regardless of the capsule they ingested (i.e., drug or placebo). At the same time, however, Δ^9-THC increased subjects' ratings of "like" effects, "feel" effects, "want more," and "high." Ratings for each of these measures peaked at around 2 h after drug administration and diminished across the session.

VAS

Drug, but not group, increased VAS ratings. Ratings on all four VAS scales increased with dose. Ratings of "stimulated" peaked at 2 h post capsule ingestion and decreased across the session. Ratings of "anxious" peaked between 1.5–3 h postingestion and decreased thereafter. Although ratings of "anxious" increased with dose, these increases were very small (see Fig. 3). Ratings of "hungry" peaked at around 2 h postingestion and then sharply declined, probably because subjects consumed a snack 2 h postingestion. In contrast to ratings of "stimulated," which declined after the first 2 h, ratings of "sedated" increased across session time.

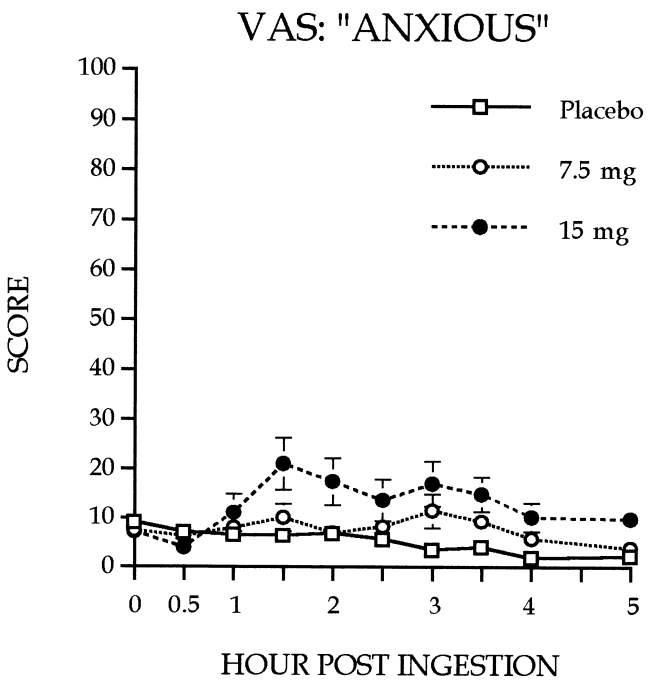

FIG. 3. Means and standard errors for VAS ratings of "anxious," shown for each hour and for each session. Data are shown for both groups combined.

ARCI

Both drug and group affected scores on several ARCI scales. On the MBG (euphoria) scale, group INF reported higher ratings than did group NON subjects following placebo and both doses of Δ^9-THC (main effect of group; see Fig. 4). Regardless of group, Δ^9-THC affected ratings on four other scales in a dose-dependent manner. Ratings on the LSD, M, and PCAG scales increased with dose, whereas ratings on the BG scale decreased with dose. For the LSD and M scales, peak ratings were observed between 1.5–2 h postingestion and decreased throughout the remainder of the session. Ratings on the PCAG scale increased across the session, whereas ratings on the BG scale decreased across the session.

Heart Rate

Both drug and group affected heart rate. For both groups, Δ^9-THC increased heart rate in a dose-dependent manner. Additionally, group INF, compared with group NON, had higher heart rates following placebo and both doses of Δ^9-THC (marginally significant dose × hour × group interaction; see Fig. 5).

DSST

Drug, but not group, affected DSST performance. Δ^9-THC produced a dose-dependent, but modest, performance deficit (compared with placebo). This effect was observable at around 2 h postingestion, the time that most other observed drug effects were at their peak.

EOS

Drug and group affected responses on the EOS. When asked if they would take the drug again, following both doses

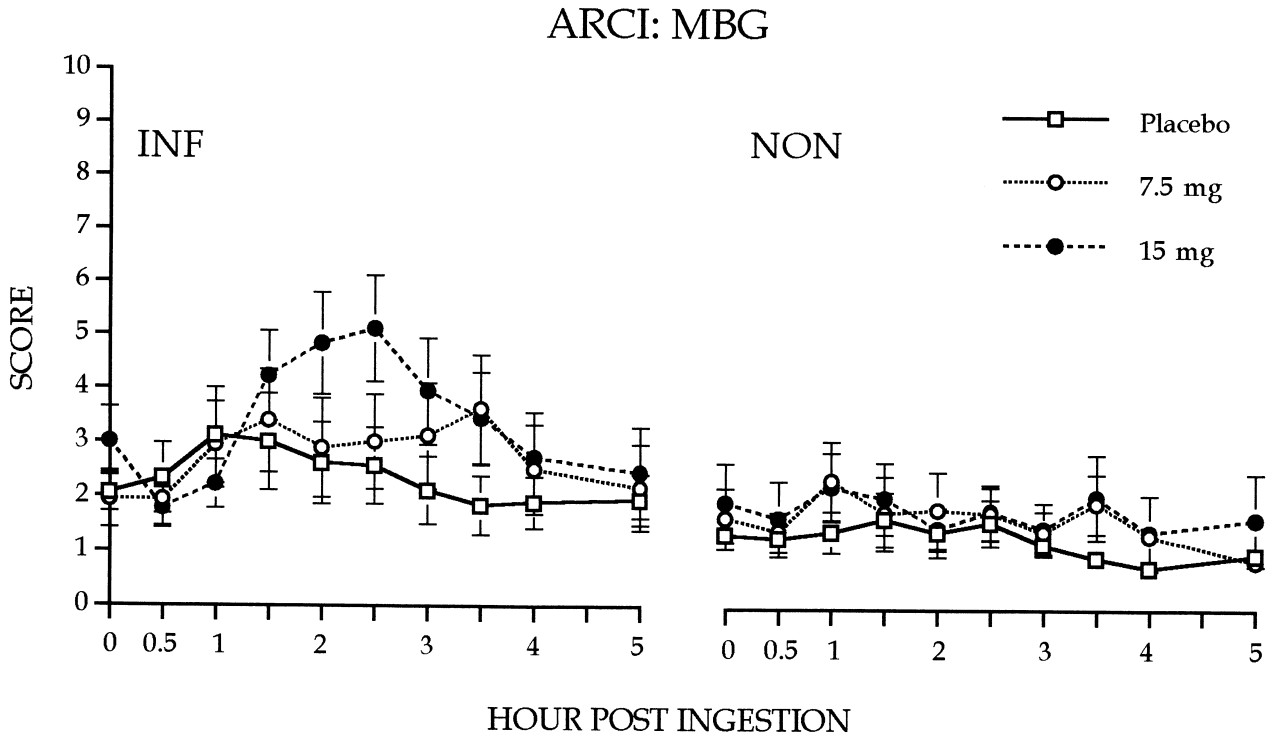

FIG. 4. Group means and standard errors for scores on the ARCI MBG scale, shown for each hour and for each session. The left panel shows means for group INF and the right panel shows means for group NON. Scores on this scale can range from 0–16.

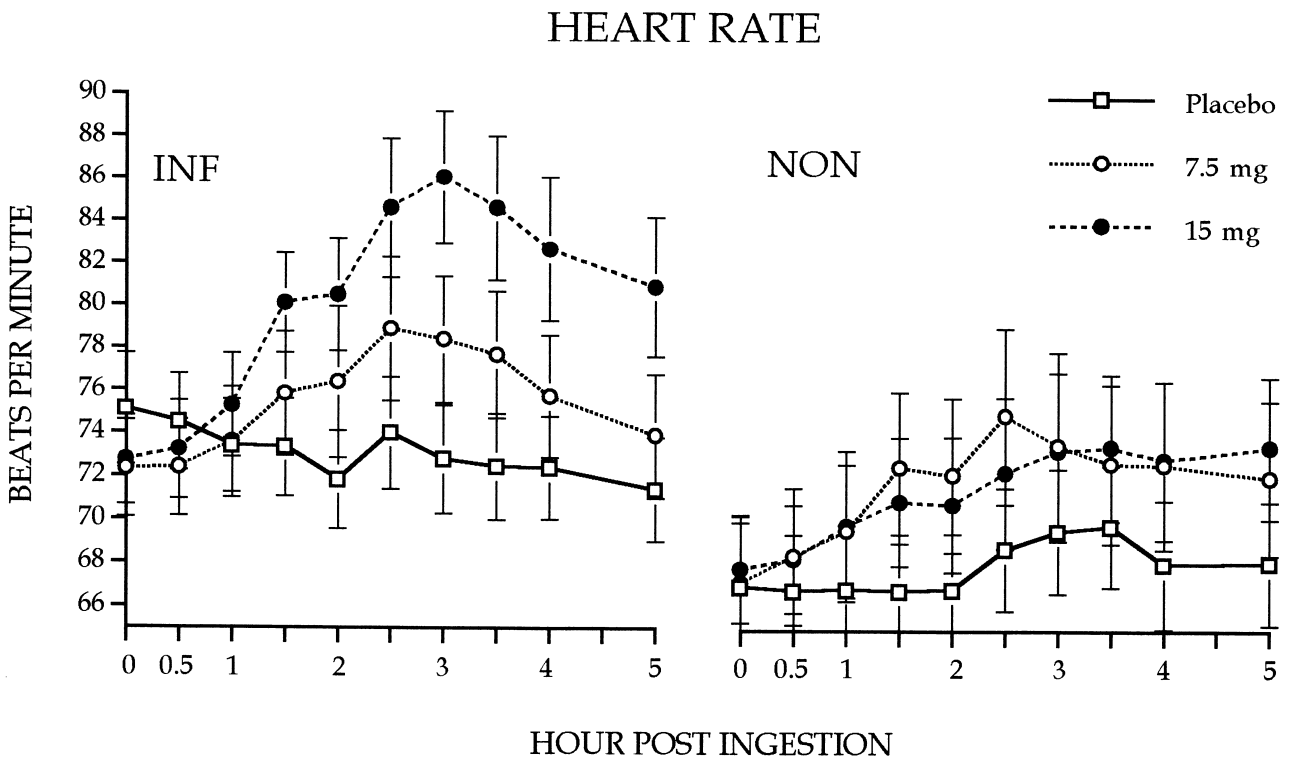

FIG. 5. Group means and standard errors for heart rate, shown for each hour and for each session. The left panel shows means for group INF and the right panel shows means for group NON.

of Δ^9-THC, the majority of Group INF subjects reported "yes," whereas the majority of group NON subjects reported "no" (see Fig. 6). Δ^9-THC produced dose-dependent increases in both groups' overall ratings of "feel" and "like." Groups INF and NON reported very similar ratings and differences between groups were not statistically significant.

DISCUSSION

As hypothesized, subjects who were told that they would receive a cannabinoid reported higher ratings on certain measures of subjective drug effects when they received oral Δ^9-THC. Specifically, the informed group reported higher ratings on visual analog scales of "like" effects and "want more" drug, higher scores on the ARCI's MBG scale, which measures euphoria, and a greater desire to take the drug again. Interestingly, the instructional conditions did not affect other qualitative measures of the drug's subjective effects, such as stimulation and sedation. This suggests that expectancy influenced subjects' liking, or affective ratings, of the drug without changing the nature or magnitude of the subjective effects. That is, subjects experienced essentially the same qualitative drug effects from oral Δ^9-THC regardless of their expectancies, but those who expected to receive a cannabinoid liked the effects more than those who did not have this expectancy. On the measure of "want more" drug, the informed subjects exhibited higher ratings regardless of whether they received active drug or placebo. Thus, this measure reflected an expectancy effect that did not interact with the pharmacological effects of the drug.

It is not clear exactly why subjects' liking of the oral Δ^9-THC was higher in the informed condition. Cannabinoids, including both oral Δ^9-THC and smoked marijuana, occasionally produce feelings of anxiety [e.g., (2)]. It is possible that these unpleasant feelings of anxiety are attenuated when subjects know the identity of the drug they are receiving, thus in-

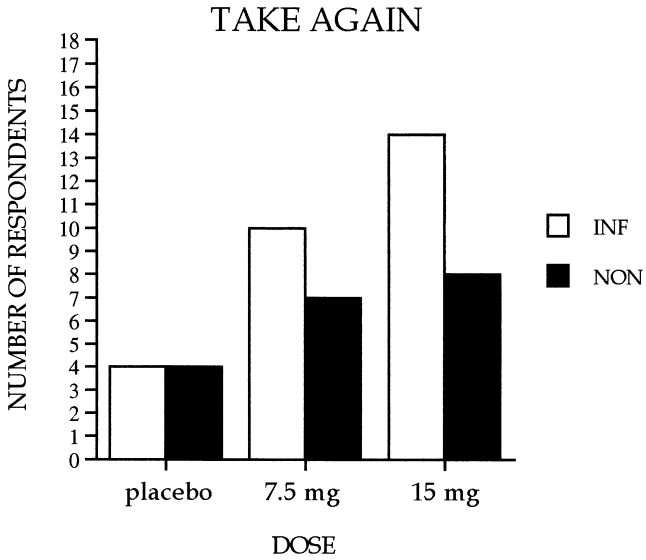

FIG. 6. Number of subjects reporting on the EOS that they would take the drug again. Open bars represent group INF (n = 18) and filled bars represent group NON (n = 17).

creasing their overall liking of the experience. However, in the current experiment, there was no evidence for increases in anxiety in either condition, making it unlikely that anxiety reduction was responsible for the observed increases in self-reported liking. It is also possible that prior information about the identity of an ingested drug increases its euphorigenic effects, and that conversely, unexpected or novel drug effects are in part aversive. These are ideas that require further investigation.

In the present study, expectancies also influenced heart rate. Subjects who expected to receive Δ^9-THC had a greater increase in heart rate after Δ^9-THC administration than subjects who did not have this expectancy. Although Δ^9-THC is known to increase heart rate [see (5)], the interaction between expectancy and increased heart rate was not anticipated and, to our knowledge, this is the first experiment to report such an interaction. Although this finding should be interpreted with some caution, as the results are marginally significant ($p = 0.06$), it does raise the possibility that expectancies can influence physiological, as well as subjective, responses to drugs. Interactions between expectancies and physiological responses to this drug may have clinical implications for its effects in both recreational and therapeutic settings.

In both the informed and the noninformed groups, oral Δ^9-THC produced a profile of effects similar to those observed in other studies that have examined the subjective effects of cannabinoids, including smoked whole plant marijuana [see (7)]. For example, Δ^9-THC produced dose-dependent increases in "feel" drug and "high" as well as scores on the ARCI Marijuana scale. These effects are similar in many respects to the effects of whole plant marijuana (3). Also, consistent with previous studies, oral Δ^9-THC in the present study also produced dose-dependent stimulatory and sedative effects.

The current experiment is the first to examine the effects of expectancies on marijuana users' responses to oral Δ^9-THC. It was observed that subjects who were told that they would receive a cannabinoid reported greater pleasurable effects and, unexpectedly, had higher heart rates following Δ^9-THC administration than did other subjects. These results have implications for both laboratory studies of cannabinoid effects and for our understanding of drug effects in nonlaboratory contexts. In laboratory studies, instructions provided to subjects regarding the identity of the drugs can influence the observed effects. In recreational settings involving the use of smoked marijuana, it is noteworthy that subjects almost always expect to receive a cannabinoid, and are probably somewhat familiar with its psychoactive effects. In contrast, in clinical settings where oral Δ^9-THC is administered for therapeutic reasons, patients' expectancies regarding both the identity of the drug and the type of effects to be experienced, are not well controlled. The results of the present study suggest that different expectancies may affect both subjective and physiological responses to Δ^9-THC, in either recreational or clinical settings.

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