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Drug and Alcohol Dependence 59 (2000) 251–260

DRUG and ALCOHOL DEPENDENCE

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Naltrexone does not block the subjective effects of oral Δ^9-tetrahydrocannabinol in humans

Stephen R. Wachtel *, Harriet de Wit

Department of Psychiatry, The University of Chicago, MC 3077, 5841 S. Maryland Ave, Chicago, IL 60637, USA

Received 5 August 1999; received in revised form 5 October 1999; accepted 5 October 1999

Abstract

Δ^9-tetrahydrocannabinol (THC) and opioids have many common effects. In addition, some THC effects in laboratory animals can be blocked or attenuated by opioid antagonists. This suggests that opioid systems mediate or modulate some THC effects. To determine whether opioid systems mediate THC effects in humans, the effects of the opioid antagonist naltrexone on subjective responses to THC were examined in 14 marijuana users. Subjects participated in a double-blinded, cross-over design in which each subject received all combinations of naltrexone (0 or 50 mg) and THC (0, 7.5, or 15 mg). THC increased heart rate and self-reported drug effects, such as euphoria and marijuana-like effects, and decreased psychomotor performance. Naltrexone increased heart rate and decreased self-reported measures of vigor and hunger but did not alter any of the effects of THC. These results suggest that the subjective, physiological, and behavioral effects of THC in humans are not mediated through opioid systems.

Keywords: Cannabinoid; Dronabinol; Marijuana; Opioid; THC

1. Introduction

Use of marijuana and hashish has been rising steadily since the early 1990s (Johnston et al., 1998a,b; SAMHSA, 1998; CEWG, 1999). Although this recent increase in marijuana and hashish use is particularly evident in teenagers, the increase has occurred among all age groups. According to one estimate, ~80% of all illicit drug users report use of marijuana or hashish (SAMHSA, 1998). Despite this widespread use, relatively little is known about the neuropharmacology of marijuana in humans. However, interest in the basic neuropharmacology of cannabinoids has grown rapidly in the last decade since it was discovered that there are endogenous cannabinoids (Devane et al., 1992; Hanuš et al., 1993; Mechoulam et al., 1995; Felder et al., 1996) and endogenous cannabinoid receptors (Devane et al., 1988; Matsuda et al., 1990; Munro et al., 1993; Shire et al., 1995), and that the cannabinoids in marijuana bind to these G_i protein linked receptors to inhibit adenylate cyclase (Howlett, 1987; Bidaut-Russell et al., 1990; Felder et al., 1993; Vogel et al., 1993).

Of particular interest are the neurochemical mechanisms underlying the reinforcing effects of marijuana. Like many other drugs of abuse, the principal active cannabinoid in marijuana and hashish, Δ^9-tetrahydrocannabinol (THC), appears to activate central reinforcement pathways that include both dopaminergic and opioid systems [see Gardner and Lowinson (1991), Gardner and Vorel (1998) for reviews]. Indeed, THC has effects in a variety of behavioral models that are thought to reflect the pleasurable and reinforcing effects of drugs that drive drug use. THC facilitates brain stimulation reward (Gardner et al., 1988, 1989), produces conditioned place preference (Lepore et al., 1995), and has been reported by some investigators to be self-administered (van Ree et al., 1978; Takahashi and Singer 1979, 1980, 1981), though others have not found this behavior (Harris et al., 1974; Leite and Carlini, 1974). Similar to most drugs of abuse, THC also appears to facilitate dopamine neurotransmission. THC both increases the activity of dopamine neurons

* Corresponding author. Tel.: +1-773-8341449; fax: +1-773-7026454.

E-mail address: swachtel@yoda.bsd.uchicago.edu (S.R. Wachtel)

0376-8716/00/$ - see front matter
PII: S0376-8716(99)00127-1

(French, 1997; French et al., 1997; Diana et al., 1998; Gessa et al., 1998) and enhances dopamine release from dopamine terminals in the nucleus accumbens, caudate putamen, and prefrontal cortex (Ton et al., 1988; Sakurai-Yamashita et al., 1989; Chen et al., 1990b, 1991) as well as from dendrites in the ventral tegmental area (Chen et al., 1993). Interestingly, THC-induced increases in dopamine efflux in the nucleus accumbens are blocked by both naloxone and naloxonazine, an antagonist specific for μ_1 opioid receptors (Chen et al., 1990a; Gardner et al., 1990; Tanda et al., 1997), suggesting that the effects of THC on dopamine systems may be mediated by opioid systems.

There is other evidence that suggests endogenous opioid systems may be involved in the effects of THC. First, THC and opioids have many common effects. Similar to opioids, THC produces sedation, hypothermia and analgesia (Holtzman et al., 1969; Noyes et al., 1975; Sofia et al., 1975; Wilson and May, 1975; Beardsley et al., 1987), inhibits intestinal motility (Anderson et al., 1975), facilitates brain stimulation reward (Gardner and Vorel, 1998), and elicits a biphasic effect on locomotor activity (Davis et al., 1972). Second, opioid antagonists block or attenuate many THC-induced effects including THC-induced analgesia and hypothermia (Tulunay et al., 1981), THC-induced facilitation of brain stimulation reward (Gardner et al., 1989; Gardner and Lowinson, 1991) and locomotor depression (Tulunay et al., 1982). Third, there are reciprocal interactions between cannabinoids and opioid antagonists in both opioid-dependent and THC-dependent animals. Cannabinoid antagonists induce withdrawal in opioid-dependent rats (Navarro et al., 1998) and naloxone precipitates opiate-like withdrawal behaviors in THC-tolerant rats (Kaymakcalan et al., 1977). Similarly, THC prevents withdrawal precipitated by naloxone in morphine-dependent mice (Hine et al., 1975; Bhargava, 1976). These findings suggest that endogenous opioids play a role in some of the effects of THC in laboratory animals.

The interactions between endogenous opioid systems and cannabinoids have not been investigated in humans. The purpose of the present study was to explore the role of endogenous opioid systems in the subjective effects of THC in humans. In the present study, the physiological and self-reported subjective effects of dronabinol (Marinol®, 7.5 or 15 mg), synthetically derived THC, were assessed in regular marijuana users pretreated with either naltrexone (Revia®, 50 mg) or placebo. Naltrexone is a potent and long-lasting opioid antagonist (Resnick et al., 1971; Martin et al., 1973). Naltrexone plasma levels peak $\sim$1 h after oral administration and remain elevated for more than 48 h after an acute dose (Verebey et al., 1976; Wall et al., 1981).

2. Methods

2.1. Subjects

Participants were male and female volunteers (n = 14) who were recruited from the surrounding 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) and both an electrocardiogram and a physical examination. To participate, subjects had to report use of marijuana/hashish for at least 1 year, use of marijuana/hashish at least ten times in their lifetime and use of marijuana/hashish in the prior 2 months. The demographics and drug use histories of the participants are summarized in Table 1.

The study was approved by the Institutional Review Board of The University of Chicago. Prior to participation in the study, subjects attended an orientation session to obtain written informed consent and to familiarize the subjects 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 listed the classes of drugs the subjects may receive: stimulant, antipsychotic, sedative, anti-opioid, cannabinoid (marijuana), and placebo. In addition, the consent form included an extensive list of potential side-effects that these drug classes may induce. Subjects were instructed to refrain from other drug use, and to keep their consumption of caffeinated beverages and nicotine to a minimum prior to each session. Subjects were also instructed not to eat after 16:00 h on the day of each session. After completing the study, subjects were debriefed and paid for their participation.

2.2. Design

The study utilized a placebo-controlled, within-subject, cross-over design. Each subject participated in six separate experimental sessions as follows: placebo/placebo; placebo/7.5 mg THC; placebo/15 mg THC; naltrexone (50 mg)/placebo; naltrexone/7.5 mg THC and naltrexone/15 mg THC. The drugs were administered double-blind and sessions were conducted at 3–4-day intervals, in randomized order.

2.3. Procedure

Each experimental session was conducted from 16:45 h to 23:15 h in the Human Behavioral Pharmacology Laboratory at The University of Chicago Hospitals. Upon arrival for each session, subjects provided a urine sample for drug and pregnancy screening. In addition, breath alcohol level (BAL) was determined to verify that each subject was ethanol-free. At 16:45 h, a technician assessed baseline vital signs and psychomotor performance, and subjects completed a series of baseline mood and drug effects questionnaires (see below). At 17:00 h, each subject ingested a capsule with 100 ml of water that contained either placebo or 50 mg naltrexone. At 17:45 h vitals signs, psychomotor performance, and subjective effects were assessed, and at 18:00 h each subject ingested a second capsule containing either placebo, 7.5 mg THC, or 15 mg THC. For the remainder of the session, data were collected for each of the dependent measures at 1-h intervals. A snack was provided at 21:00 h. At the last time point, 23:00 h, subjects completed an end of session questionnaire in addition to the other dependent measures.

Table 1
Subject demographic and drug use summary ($n = 14$)

Age (years)	
Range	18–29
Mean ± S.D.	21.7 ± 3.2
Weight (lbs; mean ± S.D.)	142.6 ± 22.6
Sex (n)	
Male	8
Female	6
Race	
Caucasian	9
African–American	2
Hispanic	2
Native American	1
Marital status (*n*; married)	1
Education (n)	
Partial college	12
College degree	2
Advanced degree	0
Full time students (*n*)	12
Current drug use (mean ± S.D.)	
Alcohol (drinks/week)	5.5 ± 6.3
Caffeine (drinks/week)	6.5 ± 5.0
Cigarettes (cigarettes/day)	5.6 ± 5.0
Marijuana (cigarettes/day)	1.7 ± 1.5
Lifetime drug use	
Stimulants (*n*; ever used)	10
Tranquilizers (*n*; ever used)	3
Hallucinogens (*n*; ever used)	10
Opiates (*n*; ever used)	5
Marijuana	
Never used (*n*)	0
Used <10 times (*n*)	0
Used 10–50 times (*n*)	1
Used >50 times (*n*)	13
Inhalants (*n*; ever used)	7

Groups of two to four subjects were tested in a laboratory designed to resemble a comfortable living room. The room contained sofas, tables, a television and VCR, a radio, and a selection of popular games. At times when no dependent measures were being collected, subjects were allowed to engage in recreational activities such as watching movies, reading, and playing games but they were not allowed to work or study. Following each session, subjects were transported home.

2.4. Dependent measures

Blood alcohol level was estimated by breath alcohol level (BAL) that was assessed using an Alco-Sensor III hand-held breathalyzer (Intoximeters, St. Louis, MO). Blood pressure and heart rate were assessed using a Digital Blood Pressure Monitor HEM-706 (Omron Healthcare, Vernon Hills, IL). 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.

Drug and mood effects were evaluated using a series of pencil and paper questionnaires that are sensitive to the dose-related effects of a variety of psychoactive drugs (Foltin and Fischman, 1991). Subjective drug effects were determined using a 53-item version of the Addiction Research Center Inventory (ARCI; Martin et al., 1971). The ARCI contains 53 true or false statements sensitive to the effects of several drug classes. This version has six empirically derived scales: the marijuana 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 dysphoric and somatic symptoms. In addition to the ARCI, subjects rated subjective 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 felt each adjective from 'not at all' on the left end of the scale to 'extremely' on the right end of the scale. The DEQ contained four 100-mm visual analog scales that the subjects used to mark their response to the follow-

ing 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 asses how much the subjects 'want' the drug.

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).

At the end of each session, participants also completed an End-of-Session Questionnaire (EOS) that contained questions regarding the overall experience of the entire session. The first question asked the subjects to rate the overall drug effect from 1, no effect, to 5, a very strong effect. The second question used the same 100-mm visual analog scale as on the DEQ to assess the extent to which the drug was 'liked' overall. The third item asked the subject to choose which of the six drug classes listed on the consent form that they think they received based on the effects they experienced. The fourth question asked the subjects if they would take the drug again. The last item gave the participants the opportunity to comment on anything that they felt might be relevant to the study, based on that session.

2.5. Drugs

Naltrexone hydrochloride tablets (Revia®, DuPont) and THC capsules (Marinol®, Roxane) were administered in opaque-colored, gelatin capsules (size 00) with dextrose as filler. Placebo capsules contained only dextrose.

2.6. Data analysis

The data for each dependent measure was analyzed with a three-way, repeated-measures analysis of variance (ANOVA). The three factors in the analysis were naltrexone, THC, and hour (time within the session). EOS data were analyzed using two-way, repeated measures ANOVA, with naltrexone and THC as the two factors. Post-hoc comparisons limited to dose and time dependent comparisons were conducted with the Fisher least significant difference test. The significance level for all statistical tests was set at $P < 0.05$.

3. Results

The significant main effects and interactions from the analysis of each dependent measure are presented in Table 2.

3.1. Vital signs

THC increased heart rate (THC by hour interaction; Table 2). Both the 7.5- and 15-mg doses of THC elevated heart rate beginning 120 min after THC administration and this effect lasted through the 300-min time point. The increase in heart rate after the 15-mg dose of THC was greater than the increase after the 7.5-mg dose at time points 180 and 240 min after administration. Naltrexone increased heart rate 240 and 360 min after its administration. However, there was no interaction between the effects of naltrexone and THC on heart rate. Neither THC nor naltrexone affected either systolic or diastolic blood pressure.

3.2. DSST

The 7.5-mg THC dose produced a slight decrease in DSST performance ($P = 0.06$) while the 15-mg dose significantly reduced performance on this task ($P < 0.05$). Naltrexone also impaired performance on the DSST, but only at time-points 180 and 300 min after its administration. There was no interaction between naltrexone and THC.

3.3. Self-report measures

The effects of naltrexone and THC on self-reported measures of drug effects on the items of the DEQ are presented in Fig. 1. THC induced a dose and time dependent increase on reports of both feeling a drug effect and experiencing a drug high. Naltrexone had no effect on either of these measures and did not alter the THC-induced increases in subjects' responses. Naltrexone and THC produced opposite effects on subjects' reports of wanting more drug. Whereas THC significantly increased ratings on this measure, naltrexone reduced ratings of wanting more drug. However, naltrexone did not alter the increased response to wanting more drug elicited by THC. Neither THC nor naltrexone alone nor any combination of these drugs significantly changed ratings of drug liking.

THC induced a dose and time dependent increase in marijuana-like effects as measured on the Marijuana scale of the ARCI (Fig. 2) and dysphoric effects as indicated by the LSD scale. However, the greater effect of the 15-mg THC dose over the 7.5-mg THC dose was only evident at later time points, 180–300 min after administration. THC also elicited a dose and time dependent increase in euphoria as measured on the

Table 2
Significant *F*-values (ANOVA) for main effects and interactions of Naltrexone (NAL), Δ^9-tetrahydrocannabinol (THC), and hour (time within session)

Dependent measure	NAL	THC	Hour	NAL × THC	NAL × hour	THC × hour	NAL × THC × hour
Vital signs							
Heart rate	19.53***	9.18**	9.50***		2.26*	2.93**	
Systolic BP			3.06**				
Diastolic BP							
DSST		3.45*	2.59*		2.33*		
DEQ							
Feel		19.63***	17.67***			7.62***	
Like							
High		19.32***	12.48***			7.04***	
More		6.02**	3.81**		2.74*		
ARCI							
A						1.91*	
BG		4.56*	3.22**				
LSD		5.87**	9.59***			3.66***	
MBG						4.94***	
PCAG			4.01**				
Marijuana		9.21***	12.85***			6.37***	
POMS							
Anger			2.36*				2.18*
Anxiety							2.25*
Confusion			2.78*				
Depression			3.10**				2.77**
Elation							
Fatigue							
Friendliness			4.58***				
Vigor	7.52*		4.37***				
Arousal			3.84**				
Positive mood						2.03*	
VAS							
Anxious							
Down							
High		16.49***	12.49***		2.24*	6.61***	
Hungry	10.61**		5.62***				
Nauseated		$P = 0.064$	3.62**				
Sedated			4.74***				
Stimulated		$P = 0.057$	3.16**			$P = 0.089$	
EOS							
Overall effect		31.00***	–		–	–	–
Overall liking		4.46*	–		–	–	–

* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

MBG scale of the ARCI (Fig. 2) and stimulant-like effects measured on the A scale of the ARCI. For both these scales, the 7.5-mg dose of THC elicited a more pronounced increase than the 15-mg dose at earlier time points, 60–180 min after administration of THC. THC elicited a decrease in arousal as measured on the BG scale. However, only the high dose elicited this effect ($P < 0.01$). Naltrexone did not alter any of the THC-induced effects.

THC increased scores of feeling 'high' on the VAS, but scores of 'high' at the 15-mg dose only exceeded scores of the 7.5-mg dose at 240 min after administration. There was also a time dependent effect of naltrexone on the high measure of the VAS, but the effect was not consistent across time points. The THC-induced increase on the VAS high measure was not affected by naltrexone. Naltrexone significantly decreased hunger ratings on the VAS (Fig. 3), but neither THC nor naltrexone, nor an interaction between the drugs affected any of the other VAS items. Although it did not reach statistical significance, there was a trend ($P = 0.064$) for an interaction between naltrexone and THC

for increasing scores on the nauseated scale, particularly with the combination of naltrexone and the 15-mg dose of THC (Fig. 3). Finally, there were time dependent increases across the session on the VAS items of 'hungry', 'nauseated', 'sedated', and 'stimulated' that were independent of drug effects.

On the POMS, there was a significant three-way interaction on the Anger, Anxiety, and Depression scales of the POMS, but these effects were due to spurious baseline differences in scores across sessions. Naltrexone decreased scores on the Vigor scale of the POMS and THC appeared to prevent a time-dependent decrease on the Positive Mood scale, but these mood effects were small compared to changes in other measures of drug effects.

THC produced a dose dependent increase in subjects' reports of the overall drug effect on the EOS (Fig. 4). On this questionnaire, unlike the momentary liking ratings, subjects reported liking the overall drug effect on the EOS. However, the liking ratings were not different at the two doses of THC (Fig. 4). There was no effect of naltrexone on EOS measures of overall drug effect or liking the drug effect and naltrexone did not alter the THC-induced increases on these EOS measures.

4. Discussion

The results of the present study did not provide evidence that endogenous opioid systems mediate the effects of THC in humans. Although naltrexone increased heart rate and decreased subjects' self-reported hunger and vigor, indicating that it was behaviorally active, it did not alter the physiological, psychomotor, or self-reported subjective effects of THC (7.5 or 15 mg). The failure of opioid antagonism to alter these effects of THC in humans is contrary to reports that opioid antagonists block or reduce the behavioral and neurochemical effects of THC in laboratory animals, including THC-induced facilitation of brain stimulation reward (Gardner et al., 1989; Gardner and Lowinson, 1991) and locomotor depression (Tulunay et al., 1982) in rats.

The reasons for the apparent discrepancy in effects of opioid antagonists in the current study and previous studies with THC in laboratory animals are unclear. It could be related to doses of drugs used, the dependent measures studied, or to differences between humans and laboratory animals. First, animal studies typically utilize higher doses of THC and opioid antagonists. Although it would be expected that the effects of lower THC doses in humans compared to animals would be

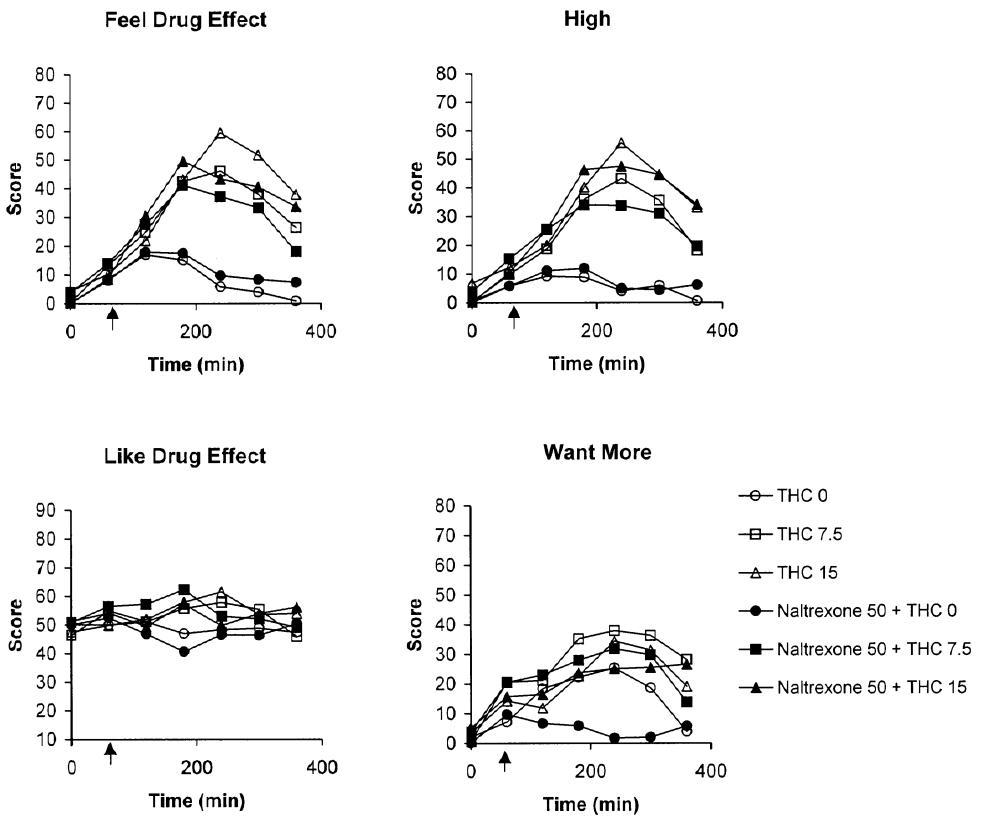

Fig. 1. Subjects' responses on the Drug Effects Questionnaire (DEQ). Responses were recorded on 100-mm VAS scales. Naltrexone (50 mg) was administered at time 0 min. THC (0, 7.5 or 15 mg) was administered at the arrow (60 min after naltrexone). Data points represent the mean ($n = 14$) at each time point. Error bars have been omitted for clarity.

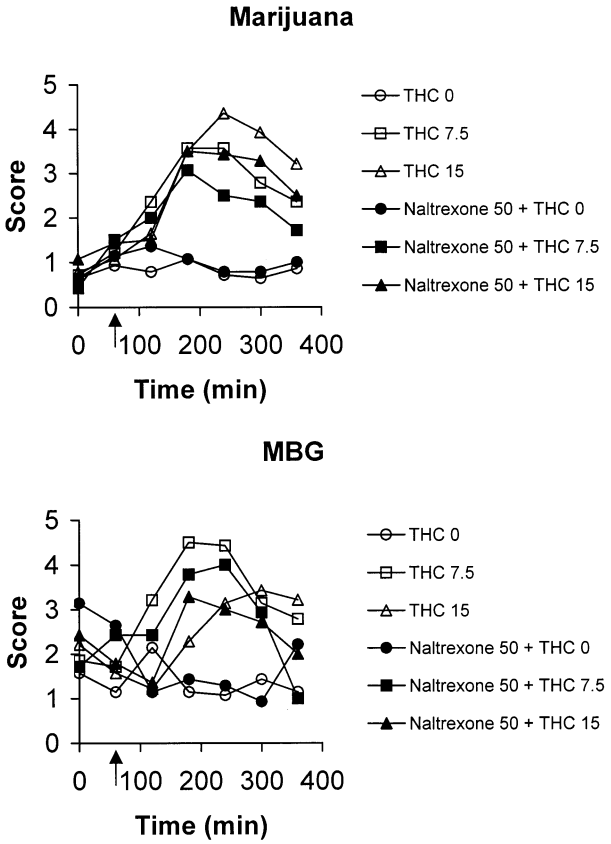

Fig. 2. Subjects' self-reported drug effects on the Addiction Research Center Inventory (ARCI) Marijuana (top) and MBG (bottom) scales. Naltrexone (50 mg) was administered at time 0 min. THC (0, 7.5 or 15 mg) was administered at the arrow. Data points represent the mean ($n = 14$) at each time point. Error bars have been omitted for clarity.

more readily antagonized, it is possible that higher doses of naltrexone may have attenuated some of the effects of THC in the present study. However, the subjective effects induced by naltrexone itself at higher doses would make it difficult to interpret the results. Second, THC and naltrexone were both administered orally in the present study. In animal studies the drugs are typically administered either intravenously or intraperitoneally. Thus, there may be pharmacokinetic factors that influence the differential results. Third, despite the similarities in the localization of cannabinoid receptors between species (Herkenham et al., 1990, 1991), there may differences in the interaction between opioid and cannabinoid systems. In fact, there are documented differences in opioid modulation of THC-induced facilitation of brain stimulation reward and dopamine release even between different strains of rats (Castaneda et al., 1991; Chen et al., 1991; Lepore et al., 1996). Finally, although none of the THC-induced alterations of the dependent measures in the present study were affected by naltrexone, opioid antagonism may have affected other measures of THC effects not measured in this study. However, the present study included measures of the most prototypic subjective and behavioral effects of THC.

There are examples of preclinical studies in which opioid antagonists failed to block or antagonize certain effects of THC. For example, naloxone neither blocks nor attenuates the increase in the firing rate of dopamine cells observed after administration of THC (French et al., 1997; Diana et al., 1998; Gessa et al., 1998). This suggests that the role of the endogenous opioid system, and its interaction with the dopamine system, in mediating the behavioral effects of THC is complex.

In summary, pretreatment with the opioid antagonist naltrexone neither blocked nor reduced the THC-induced increase in heart rate, decrease in psychomotor performance, or changes in mood and self-reported drug effects. This suggests that these effects of THC in humans are not extensively regulated by endogenous opioid systems. Moreover, because naltrexone failed to attenuate the pleasurable or euphoric effects of THC, it is unlikely that naltrexone could be used to treat compulsive marijuana use. However, the current results do not preclude the possibility that opioid systems may modulate other effects of THC in humans.

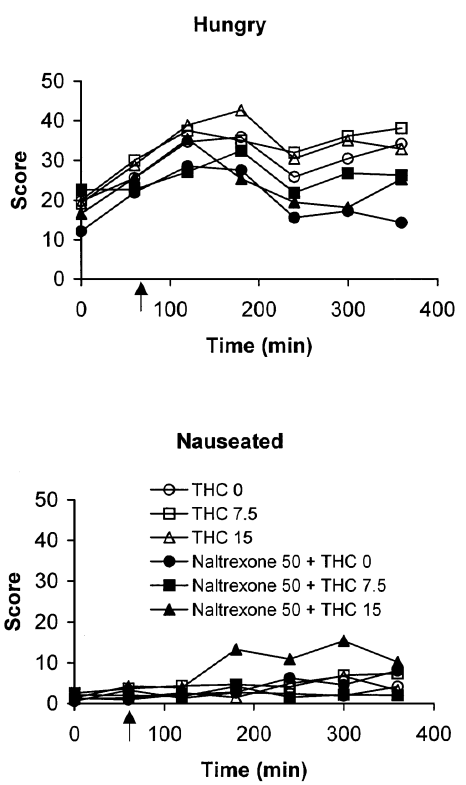

Fig. 3. Subjects' responses to the 100-mm Visual Analogue Scale (VAS) items hungry (top) and nauseated (bottom). Naltrexone (50 mg) was administered at time 0 min. THC (0, 7.5 or 15 mg) was administered at the arrow. Data points represent the mean ($n = 14$) at each time point. Error bars have been omitted for clarity.

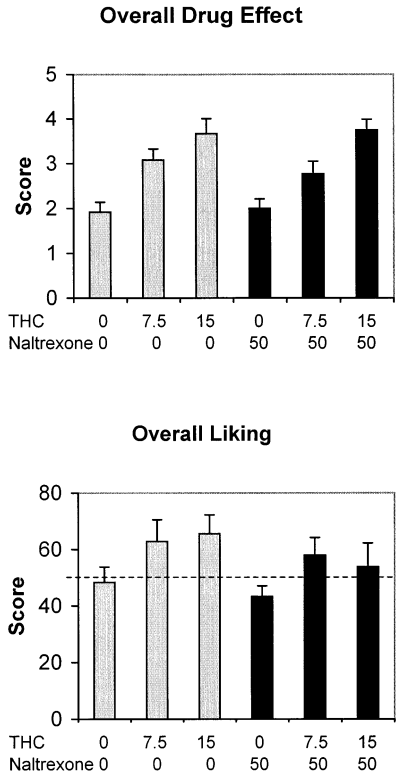

Fig. 4. Subjects' End of Session (EOS) self-reports of overall drug effect (top) and liking the drug effect (bottom) across each session. Doses of naltrexone and THC are mg values. Bars represent the mean ± S.E.M. ($n = 14$) for each drug condition.

Acknowledgements

The authors wish to thank Chris O'Connor, Aaron York, Paul Meyer and Almeta Woods for their technical assistance. This work was supported by USPHS Grant RO1 DA03517.

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