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Antinociceptive, subjective and behavioral effects of smoked marijuana in humans

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Abstract

The purpose of this study was to determine whether marijuana produced dose-dependent antinociception in humans and, if so, whether endogenous opiates modulate this effect. A total of five male regular marijuana users participated in three test sessions during which they smoked cigarettes containing 0% (placebo) and 3.55% Δ^9-tetrahydrocannabinol (Δ^9-THC) (active). Each of four controlled smoking bouts per session, spaced at 40-min intervals, consisted of nine puffs from active and placebo cigarettes (three cigarettes, three puffs per cigarette, one puff per min). During successive bouts, participants smoked 0, 3, 6 and 9 (0, 3, 9 and 18 cumulative) puffs from active marijuana cigarettes, with the remainder of puffs from placebo cigarettes. Test sessions were identical, except for naltrexone 0, 50 or 200 mg p.o. (randomized, double-blind) administration 1 h before the first smoking bout on the different days. Before smoking, between smoking bouts and postsmoking, participants completed an assessment battery that included antinociceptive (finger withdrawal from radiant heat stimulation), biological, subjective, observer-rated signs and performance measures. Marijuana produced significant dose-dependent antinociception (increased finger withdrawal latency) and biobehavioral effects. Naltrexone did not significantly influence marijuana dose-effect curves, suggesting no role of endogenous opiates in marijuana-induced antinociception under these conditions.

Keywords: Marijuana smoking; Δ^9-Tetrahydrocannabinol; Antinociception; Analgesia; Endogenous opioids; Naltrexone; Subjective effects; Performance; Heart rate; Humans

1. Introduction

Cannabinoid receptor agonists generally produce antinociception in animals; however, the test compound, assay, species, dose and route of administration used can modulate this effect (Harris, 1971; Dewey, 1986; Adams and Martin, 1996; Martin and Lichtman, 1998). Neuropharmacological studies, most using the tail-flick assay, have begun to characterize the mechanisms of cannabinoid antinociception. Two cannabinoid receptor subtypes have been identified; CB_1 receptors (nervous system) account for most of marijuana's effects, whereas CB_2 receptors (spleen) mediate immune response (Adams and Martin, 1996). The primary brain site of tetrahydrocannabinol (THC) antinociceptive action is at CB_1 receptors in the periacqueductal gray (Lichtman et al., 1996), also a principal site of opioid antinociception (Basbaum and Fields, 1984). Cannabinoid antinociception in this region is blocked by the CB_1 antagonist SR-141716A (Lichtman and Martin, 1997; Welch et al., 1998) but not systemically administered opioid antagonists (Welch et al., 1995; Vivian et al., 1998), indicating a centrally mediated, opioid-independent mode of action. Recent studies also implicate brainstem circuitry that mediates THC, but not morphine, analgesia (Martin et al., 1998; Meng et al., 1999).

Early studies using opioid antagonists, at high doses that presumably blocked mu, kappa and delta receptors, demonstrated partial attenuation of THC-induced antinociception (Wilson and May, 1975; Tulunay et al., 1981; Ferri et al., 1986). These results suggested that

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endogenous opiates might partly mediate this effect. Subsequently, a second site of cannabinoid antinociception was identified in the spinal cord (Yaksh, 1981; Lichtman and Martin, 1991; Smith and Martin, 1992), where this effect is blocked by i.t. administration of kappa-opioid antagonists (Welch, 1993a,b; Smith et al., 1994; Reche et al., 1996) but only partially attenuated by SR-141716A (Welch et al., 1995).

Effects of THC on clinical pain have been infrequently studied in humans, with mixed results (Noyes et al., 1975, 1976; Raft et al., 1977). Analgesic effects of THC are usually overshadowed by side-effects, e.g. sedation. Cannabinoid effects on human pain sensitivity have been studied in double-blind, placebo-controlled laboratory situations, again with conflicting findings. Single doses of oral THC did not increase pain threshold using cold pressor (25 mg; Karniol et al., 1975) or electrocutaneous stimuli (12 mg; Hill et al., 1974), whereas i.v. THC (0.022 and 0.044 mg/kg) increased pain detection but not tolerance threshold using pressure and electrocutaneous stimulation (Raft et al., 1977). Acute marijuana (cigarettes with $\approx 1.0\%$ THC) versus placebo smoking did not affect radiant heat (thermode on the forearm) sensitivity in either cannabis-experienced or non-experienced volunteers (Milstein et al., 1974). These negative results may be due to the use of a single low THC dose, smoking procedures that were less well-controlled, a response criterion that was closer to a sensory than a pain threshold, and short mean reaction times (i.e. possibly indicating a ceiling effect). In contrast, Milstein et al. (1975) found significant increases in pain tolerance following marijuana smoking, with slightly (but not significantly) greater effects for cannabis-experienced than non-experienced volunteers. Clark et al. (1981) found a hyperalgesic effect of chronic daily marijuana smoking, relative to a presmoking wash-out period, during a long-term residential study.

Contributing to this uncertain body of literature is the fact that procedures for measuring human pain sensitivity are often unreliable. Lee and Stitzer (1995) developed a procedure in humans that is comparable to the tail-flick assay. This procedure, which requires the participant to withdraw the finger from a radiant heat source under pain threshold instructions, was shown to have better reliability (within- and between-sessions) than an electrocutaneous method. This is also important because THC actually lowered pain threshold (produced hyperalgesia rather than antinociception) in healthy volunteers using electrocutaneous stimulation (Hill et al., 1974). Thermal stimulation has been the predominant laboratory model for evaluating cannabinoid antinociception in animals; we therefore used this method to probe pain sensitivity in marijuana-smoking human volunteers.

This study had three aims. The first aim was to determine whether marijuana smoking produced dose-dependent thermal antinociception in humans, similar to animals. These data were compared with biological, subjective effects, objective signs and performance measures for a complete profile. Psychomotor measures were used to evaluate whether marijuana produced motor deficits versus an inhibition of pain transmission. The second aim was to extend the method of Chait et al. (1988), in which participants smoked 0, 2, 4 and 8 cumulative active (and placebo) puffs across four smoking bouts from cigarettes with 1.4% THC. In the present study, participants smoked a wider range of doses — 0, 3, 9 and 18 cumulative active (and placebo) puffs from cigarettes with 3.55% THC across four bouts. In the Chait et al. study, smoking occurred at 20-min intervals; in the present study, bouts were scheduled every 40-min to collect a broader range of data (see first aim). The third aim was to assess whether endogenous opiates influence marijuana effects in humans, i.e. whether naltrexone pretreatment produced rightward shifts in marijuana dose-response curves. Based on evidence that kappa-opioid antagonists attenuate THC-induced spinal antinociception in animals, we tested high doses of naltrexone to block a higher fraction of kappa (and other opioid) receptors. Naltrexone was used because there are no kappa-selective antagonists presently available for human use, and it has a long duration of action (Verebey et al., 1976) to span the cumulative dosing period.

2. Methods

2.1. Participants and screening

The local Institutional Review Board approved this study. All volunteers provided informed consent prior to participation. Male and female recreational drug users aged 18–45 years old were recruited by newspaper advertisements and paid for participation. Before the study, participants underwent a complete medical examination (blood chemistry, electrocardiogram, medical history, urine samples for drug analysis and pregnancy testing, physical examination) and were interviewed about their current and past psychoactive substance use using the Structured Clinical Interview for DSM-IV (SCID; First et al., 1996). Only generally healthy, regular marijuana users were included; they were required to have smoked from 3 to 20 marijuana cigarettes per week (by self-report) in the month prior to screening. Participants were excluded if they reported current illicit drug use (other than marijuana) but the majority had previous experience with other illicit drugs. Alcohol use in excess of 20 standard drinks per week, a history of drug treatment, inability to pass a

physical examination, chronic health problems, or a positive pregnancy test were all exclusionary factors.

2.2. Study design

The present study employed three different naltrexone pretreatments followed 1 h later by cumulative dose marijuana smoking and assessment. Thus, a two-way repeated measures design was used to evaluate the influence of naltrexone on marijuana effects. Session time (nine levels, within session: pre-naltrexone and post-naltrexone baselines; after 0, 3, 9 and 18 cumulative active puffs, and at 1, 2 and 3 h post-smoking) and naltrexone dose (three levels, between sessions: 0; 50 and 200 mg) were the within-subject factors. Participants were exposed to the three naltrexone dose conditions in a randomized, counterbalanced order. Fig. 1 illustrates the session timeline.

2.3. Drugs

The National Institute on Drug Abuse Research Technology Branch supplied the marijuana cigarettes. These cigarettes were ~85 mm (length) × 25 mm (circumference), weighed from 750 to 990 mg, and contained either 0% (placebo) or 3.55% (active) THC. Cigarettes were stored in a −20°C freezer until the day before use. At least 12 h before each session, moisture content of the cigarettes was raised by placing them above a saturated NaCl solution in a closed humidifier at room temperature. Marijuana doses were selected based on previous research from our laboratory (Azorlosa et al., 1992), indicating that healthy, marijuana-experienced volunteers could tolerate up to 25 puffs (one per min) from 3.55% cigarettes in a single session. Smoking was conducted under double-blind conditions.

Naltrexone tablets (DuPont, Wilmington, DE) were used to compound the study capsules. Doses of 50 and 200 mg were prepared by placing the hydrochloride powder in four identically opaque gelatin capsules and filling with lactose USP (Mallinckrodt, St. Louis, MO). Matched placebo doses consisted of identical capsules filled with lactose. Naltrexone has been safely administered to eating disorder patients at doses up to 400 mg/day (Marrazzi et al., 1997), to opioid abusers at doses up to 200 mg/day (Gonzalez and Brogden, 1988) and to polydrug abusers at 200 mg/day (Walsh et al., 1996). However, others (Hollister et al., 1981) have

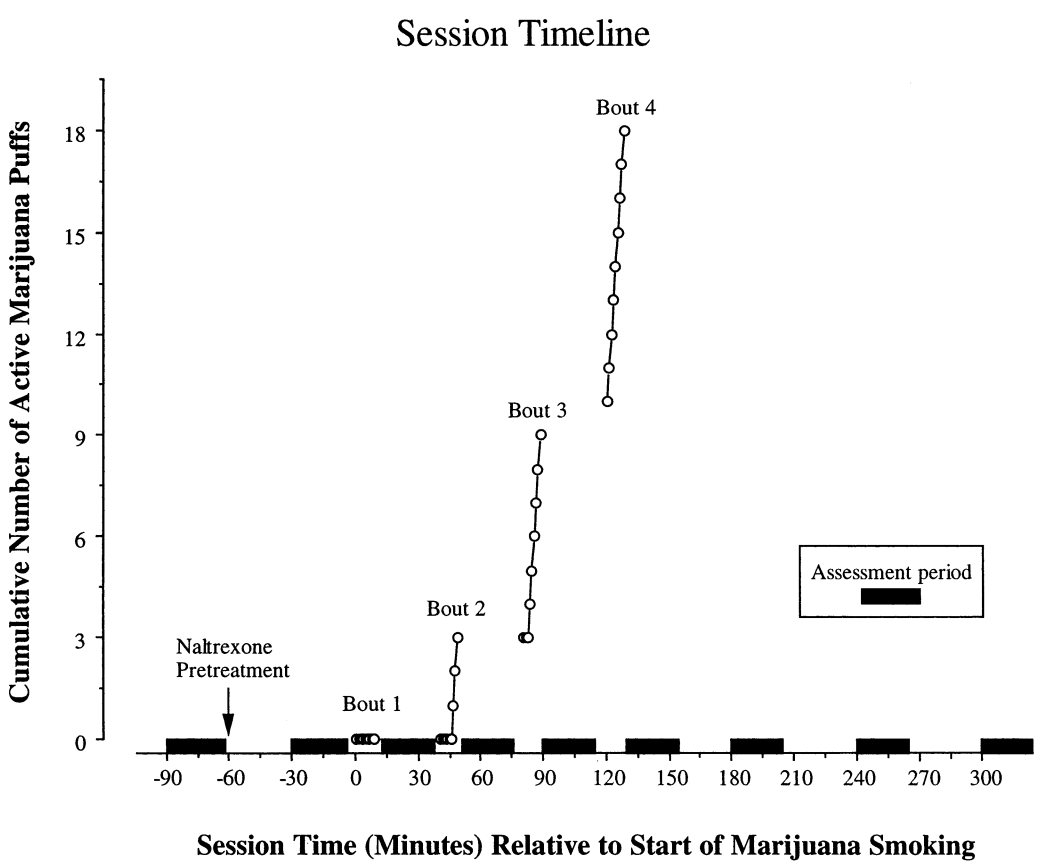

Fig. 1. Session timeline (see text for details). Naltrexone was administered 60 min before the initiation of marijuana smoking. In each smoking bout participants inhaled nine puffs (1/min; 9-min duration), with zero active puffs in bout 1, three active puffs in bout 2 (three cumulative), six active puffs in bout 3 (nine cumulative), and nine active puffs in bout 4 (18 cumulative). Assessment periods (30-min duration) were scheduled before and after naltrexone pretreatment, after each smoking bout, and at 1, 2 and 3 h after completion of smoking.

reported aversive effects of acute lower doses in healthy volunteers without drug abuse histories.

2.4. Procedure

2.4.1. Training session

Before the study, participants practiced the pain threshold sensitivity task, psychomotor performance measures and computerized questionnaires. During the pain sensitivity procedure (see below), the experimenter adjusted the heat intensity until the participant produced mean (average of left and right) finger withdrawal latencies between 6 and 8 s on three consecutive trials. For psychomotor tasks, participants had to respond consistently across three consecutive trials (defined in advance for each measure). Participants were also taught the controlled smoking procedure, which has been described in detail elsewhere (Azorlosa et al., 1992, 1995). They were trained to achieve the target puffing and inhalation behaviors using placebo cigarettes; this was designed to minimize variability in the marijuana doses delivered during the experimental sessions. Lung vital capacity was determined during this session. The training session lasted ~2–3 h.

2.4.2. Protocol timeline and experimental sessions

Participants participated in three sessions scheduled at least 3 days apart; they completed the sessions over an average of 9.2 days (range, 7–13), with comparable spacing between sessions 1 and 2 (mean 4.6 days) versus between sessions 2 and 3 (mean 4.6 days). Test sessions began at ~08:00 h. Participants were instructed to eat a light breakfast before arriving at the laboratory. Participants were instructed not to drink alcohol for 24 h or smoke marijuana for 48 h before each session. Participants were instructed to refrain from all other illicit drug use during the study. To promote compliance with these restrictions, participants provided urine samples (which were tested using EMIT for opioids, cocaine, barbiturates, amphetamines, and benzodiazepines) and breathalyzer tests before each session; none were positive. Caffeine and cigarette use was prohibited from the time of arrival at the laboratory and throughout the session, ensuring at least a 90-min period of abstinence prior to marijuana smoking; no caffeine or nicotine abstinence symptoms were reported. Participants and staff were blind to cigarette THC content and naltrexone dose.

2.4.2.1. Baseline measures. All sessions took place in a private, specially ventilated test room located at an outpatient research laboratory. The research nurse was always present during testing and smoking periods. At the start of each session, heart rate and respiratory monitoring equipment were attached to the volunteer and an i.v. catheter was inserted into an antecubital vein. Naltrexone was always administered 1 h before the start of smoking. All measures except the blood sample were collected starting 30 min before naltrexone (session baseline). Then 30 min after naltrexone, the first blood sample was obtained and all measures were repeated (presmoking baseline).

2.4.2.2. Smoking procedure. During each of the four smoking bouts, three cigarettes were used (i.e. 12 per session). Cigarettes were arranged in a tray with numbered slots to maintain proper dosing order. Participants took three puffs at 1-min intervals from each cigarette. In the minute before each new cigarette, the experimenter lit the cigarette and (after removing the old one first) placed it in the plastic holder in time for the next puff. It took ~9 min to complete each smoking bout. In bout 1, all three cigarettes were placebos (zero active puffs). In bout 2, the first two cigarettes were placebo and the last one was active (three active puffs). In bout 3, the first cigarette was placebo and the last two were active (six active puffs). In bout 4, all three cigarettes were active (nine active puffs). Thus, the volunteer took 0, 3, 9 and 18 cumulative active puffs after bouts 1, 2, 3 and 4, respectively.

Controlled smoking involved taking one 50-ml puff (over ~1.5 s) every 60 s, inhaling to a depth of ~35% of lung vital capacity (over ~2.5 s), and holding smoke in the lungs for 10 s. Actual smoking behavior recorded by the computer reached these designated targets and, when analyzed statistically, did not significantly vary over bouts or between sessions. Thus, our computerized feedback procedures prevented participants from altering their smoking behavior.

2.5. Measures

At each session time point, data were collected in the following order: biological exposure [blood, heart rate (HR), carbon monoxide (CO)], subjective effects [visual analog scales (VAS), Addiction Research Center Inventory (ARCI), multiple choice), antinociception, psychomotor performance (balance, Digit Symbol Substitution Test (DSST), divided attention, digit span], and observer-rated signs. Results are presented according to their relevance for the present hypotheses.

2.5.1. Antinociception

This procedure, a modified version of the rodent tail-flick test, has been described in detail (Lee and Stitzer, 1995). The apparatus consists of a radiant heat source, photocell, digital timer, and power source. The participant was instructed to place the distal pad of his/her index finger over a 3-mm hole, through which the heat source (projection bulb) radiated from below. Above the finger (mounted on a post) was a photocell; when the finger covered the light source, the photocell

was prevented from sensing the light. A switch activated the lamp and digital timer. Once the participant removed his/her finger the light reached the photocell, automatically stopping the light and the timer. The present procedure differs from that of Lee and Stitzer (1995) in that both the dominant and non-dominant index fingers were tested (in that order) on each trial. These two withdrawal latency values and their average were analyzed separately to determine whether the average score would be more reliable than either individual score. Pain sensitivity testing was conducted about halfway through the assessment battery, i.e. ~15 min after each smoking bout ended. Participants were instructed to retract their finger from the heat stimulus when it first became painful (i.e. pain threshold). Cut-off time was 20 s. To compare directly with previous animal studies of thermal antinociception, maximum percent effect (MPE) scores were calculated according to a standard algorithm (Harris and Pierson, 1964):

$$\text{MPE} = 100 \times [(\text{test} - \text{presmoking control}) / (20 - \text{presmoking control})]$$

2.5.2. Biological exposure

A total of five 5-ml blood samples were taken in each session to determine plasma THC levels prior to smoking and immediately after each of the four smoking bouts. Immediately after each session plasma was separated and frozen. All samples were sent in a single batch to the Research Triangle Institute (Research Triangle Park, NC) for radioimmunoassay of Δ^9-THC content in ng/ml (Cook et al., 1982). Interassay variability was within 5% when standards were run at both 8 and 30 ng/ml.

Heart rate (HR, in beats per min, bpm) was measured continuously using a pulse oximeter. HR was recorded three times — at 5, 15 and 25 min — after each smoking bout ended; the highest of these three values was used as the index of marijuana-induced tachycardia.

Expired air CO levels (in parts per million, ppm) were obtained by having participants fully inhale, exhale, inhale again, hold their breath for 15 s, and then exhale into an Ecolyzer 2000 device (Energetics Science, Elmsford, NJ). CO levels were measured before naltrexone (pre-session baseline), after naltrexone (pre-smoking baseline), immediately after each smoking bout, and at 1, 2 and 3 h after the final smoking bout.

2.5.3. Psychomotor performance

On the balance task, the participant was instructed to stand (with eyes closed) on one leg at a time until the experimenter told the participant the trial was completed; each of the two trials (right leg, then left leg) lasted 30 s. The experimenter began each trial by starting a timer when the participant lifted the leg, and ended the trial by stopping the timer when the participant put the leg down. Scores from each of the two trials were averaged to provide a duration measure of overall balance. The maximum score was 30 s at each assessment time point.

Then three computerized psychomotor tasks were performed [see Azorlosa et al. (1992) for details]. The DSST provided a measure of encoding speed and accuracy. A divided attention test provided concurrent measures of motor tracking and visual detection. A digit span (forward and reverse) provided a measure of short-term memory.

2.5.4. Subjective effects

A total of 15 separate VAS ratings were each presented on the computer monitor as a 100-mm horizontal line, anchored on the left with 'not at all' and on the right with 'extremely'. Participants moved the cursor (a vertical line) along the horizontal line with a joystick and clicked the button when they reached the position on the line that represented their current feeling (questions usually phrased, 'Do you feel ___ right now?'). Ratings (in order) were: any drug effect, good drug effect, bad drug effect, high, drunk, impaired, stoned, like the drug effect, sedated, confused, nauseous, desire more of the drug, anxious, down, and hungry. A final VAS asked participants to rate how closely the current drug effect compared with the effect from their usual smoking outside the laboratory; a rating of 0 was anchored with 'much weaker', 50 was anchored with 'same', and 100 was anchored with 'much stronger'.

To obtain an estimate of the monetary value of the marijuana doses smoked, the participant completed a multiple-choice form with 50 independent choices between drug and money. The monetary amounts ranged from \$0.25 to \$64.51, increasing by arithmetic progression from small steps (a few cents in the first choices) to large steps (a few dollars in the final choices). Unlike the standard Multiple Choice Procedure (Griffiths et al., 1993), there was no additional session to provide consequences for these drug versus money choices.

The short form of the ARCI (Martin et al., 1971) consisted of 49 true-false items. These 49 items make up five empirically determined subscales: Amphetamine (A) and Benzedrine Group (BG), both sensitive to stimulant-like effects; MBG, sensitive to euphoria; PCAG, sensitive to sedation; and LSD, sensitive to somatic and dysphoric changes. A Marijuana scale, previously reported by Chait et al. (1988), was also analyzed.

2.5.5. Observer-rated signs

A total of seven objective signs of drug effect were developed. At the end of each assessment block, the observer rated each sign on a 0–3 scale, as indicated below. These were: 'Good Mood' (0 = not at all [bad

mood], 1 = mild [pleasant, agreeable; no smile required], 2 = moderately happy [smiles], 3 = extreme [euphoric, exuberant]); 'Stimulated/Aroused' (0 = normal [quiet, calm, unaroused], 1 = mild [occasionally fidgety, restless or nervous], 2 = moderate [frequently fidgety, restless or nervous], 3 = strong [agitated or vigilant]); 'Flushed Face' (0 = normal color, 1 = mild [slight reddening], 2 = moderate [noticeable reddening], 3 = strong [patches]); 'Sweaty' (0 = normal [palms and forehead dry to touch], 1 = mild [sweat palpable on palms or forehead], 2 = moderate [see sweat on palms or forehead without touching], 3 = strong [underarms sweaty in addition to palms and forehead]); 'Nausea/Vomiting' (0 = normal [no spontaneous report of gastrointestinal disturbance], 1 = spontaneous report of nausea, 2 = 'dry heaves', 3 = vomiting); 'Red Eyes' (0 = normal [white], 1 = just detectable redness [one or both eyes], 2 = moderate redness [lines in both eyes], 3 = 'bloodshot' eyes [extensive]); and 'Strength of Drug Effect' (0 = none; 1 = mild [just detectable increase — one or two of the six signs above], 2 = moderate [multiple, mild signs of a reaction], 3 = strong [multiple, intense signs of a reaction].

2.6. Data analysis

Marijuana smoking and naltrexone pretreatment effects were analyzed using two-way Time (pre-naltrexone and post-naltrexone baselines; after 0, 3, 9, and 18 cumulative puffs, and at 1, 2 and 3 h post-smoking) × Naltrexone Dose (0, 50, 200 mg) repeated measure ANOVAs. In all analyses, Huynh–Feldt adjustments of repeated measures degrees of freedom were used to correct for violations of sphericity.

There is an extensive literature for marijuana dose-effects on most measures collected in this study (Jaffe, 1985; Chait and Pierri, 1992; Adams and Martin, 1996). Thus, following the ANOVAs, planned comparisons of each active dose condition (3, 9 and 18 puffs) versus placebo (zero puffs) were conducted using one-tailed *t*-tests whenever the direction of effect (increase or decrease) was unambiguous. To limit the number of planned tests, active doses were not compared with one another. Based on this literature and our own previous studies (Azorlosa et al., 1992, 1995), we expected that marijuana smoking would produce dose-related increases in plasma THC, CO, HR, antinociception (finger withdrawal latency), and certain subjective effects (e.g. VAS high and liking, ARCI Marijuana and PCAG subscales). We expected that marijuana would produce dose-related decreases on psychomotor measures (e.g. balance time, DSST, divided attention latency and tracking, digit span). Because observer-rated signs were created for the present study, two-tailed Tukey post hoc tests were used.

3. Results

3.1. Participant characteristics

A total of 13 participants (nine male, four female) aged 19–27 enrolled in the study and participated in at least the first experimental session. A total of eight (four male, four female) were terminated after the first session. All four females disliked the strength of the marijuana effect. Among the four males, one could not tolerate the blood withdrawal procedure, one coughed excessively which disrupted the controlled smoking procedure, one disliked the strength of the marijuana effect, and the other experienced gastric upset, blurred vision and muscle weakness during the combination of naltrexone 200 mg and marijuana smoking. Aside from being female, no other demographic or drug use factors were obviously associated with study attrition. A total of five male (four white, one Asian American) volunteers completed the remaining sessions. These volunteers had a mean age of 20.6 years, averaged 14 years education, and reported having smoked marijuana for an average of 4 years; four were current cigarette smokers. Participants reported usually smoking 6–12 marijuana cigarettes per week.

3.2. Cumulative marijuana smoking effects

As Table 1 indicates, marijuana smoking produced statistically significant, dose-related effects across a wide range of measures. In contrast, naltrexone pretreatment at either active dose (relative to placebo) did not systematically influence marijuana dose-effect curves.

3.2.1. Antinociception

Mean finger withdrawal latency (Fig. 2) was stable before smoking. Relative to presmoking, finger withdrawal latency did not significantly increase after zero or three active puffs, increased slightly (but not significantly) after nine active puffs, and was significantly greater after 18 active marijuana puffs. The 18 active-puff condition was significantly different from the zero and three active-puff conditions in planned comparison tests. Nevertheless, the significant difference between 18-puff and presmoking control levels was rather modest in size (19% MPE; see right ordinate). At the first post-smoking time point, mean finger withdrawal latency returned to baseline levels. The apparent rebound effect, i.e. decrease below presmoking baseline, at the last two postsmoking time points was not significantly different than presmoking baseline but was different from the 18 active-puff condition.

The marijuana dose-effect curves for the dominant and non-dominant finger withdrawal latencies were highly similar and each was significant (Table 1), i.e.

Table 1
Summary of statistical effects

Measure	Time[a], F[8,32]	Time × pretreatment, F[16,64]	Active marijuana condition means				
			BL	0-puff	3-puff	9-puff	18-puff
Antinociception (s)							
Dominant	4.16 (0.02)	NS	7.0	7.6	7.3	8.6	9.3
Non-dominant	4.56 (0.02)	NS	6.6	7.5	7.6	8.1	9.1
Average	4.95 (0.02)	NS	6.8	7.6	7.5	8.4	9.2
Biological exposure							
Plasma THC (ng/ml)[b]	32.11 (0.0001)[c]	NS	3.4	4.8	161	179	202
Expired CO (ppm)	32.77 (0.0001)	NS	5.9	15.9	19.7	25.4	30.3
Heart rate (bpm)	22.30 (0.0001)	NS	66.1	69.3	82.4	89.2	93.1
Psychomotor performance							
Balance (s)	5.77 (0.001)	NS	28.6	28.6	26.6	22.4	16.2
DSST # attempts	10.90 (0.002)	NS	74.0	73.5	74.8	71.3	67.1
DSST # correct	10.83 (0.0001)	NS	70.8	70.7	71.9	67.3	64.1
DSST % correct	NS	NS	0.96	0.96	0.96	0.94	0.96
Div. attn. latency (s)	2.40 (0.04)	NS	1.08	1.08	0.98	1.00	1.14
Div. attn. distance (pixels)	NS	NS	9.7	10.0	11.3	11.8	15.8
Digit span # correct	1.90 (0.10)	NS	10.5	10.5	10.2	9.6	9.2
Digit span longest	2.13 (0.08)	NS	14.4	14.3	14.2	13.7	13.3
VAS ratings (0–100)							
Any effect	30.52 (0.0001)	NS	0.0	5.5	38.9	62.7	71.8
Good effect	26.78 (0.0001)	NS	0.0	5.1	44.8	67.5	71.5
Bad effect	3.22 (0.01)	NS	0.0	0.0	3.8	2.3	10.0
High	31.13 (0.0001)	NS	0.0	4.9	39.2	60.6	69.7
Impaired	10.54 (0.005)	NS	0.0	1.2	21.3	37.1	46.1
Stoned	25.67 (0.0001)	NS	0.0	3.1	36.3	58.0	62.4
Liking	25.77 (0.0001)	NS	0.0	8.9	49.5	65.1	63.8
Sedated	4.57 (0.03)	NS	0.0	2.0	17.9	22.3	34.9
Confused	NS	NS	0.0	0.4	5.2	8.1	18.8
Nauseous	NS	NS	0.0	0.0	3.7	1.1	5.1
Desire	4.69 (0.005)	NS	4.9	20.5	45.7	42.5	28.2
Anxious	NS	NS	1.2	0.0	13.9	18.9	22.5
Down	6.08 (0.01)	NS	0.0	0.0	5.3	3.5	12.5
Hungry	17.14 (0.0001)	NS	3.2	5.0	17.3	33.3	49.0
Comparison	19.13 (0.0001)	NS	0.0	6.2	42.3	62.6	71.1
Multiple choice form ($)	6.32 (0.002)	NS	0.25	0.98	4.95	11.62	9.97
ARCI scales							
Marijuana	11.96 (0.0001)	NS	0.0	0.6	3.7	5.5	5.3
PCAG	7.60 (0.0001)	NS	3.3	3.5	3.9	4.7	5.9
MBG	7.02 (0.0001)	NS	0.7	1.7	3.7	4.7	3.4
AMPH	5.54 (0.01)	NS	1.3	2.1	3.3	3.9	3.7
LSD	4.53 (0.02)	NS	3.1	3.0	5.2	5.6	6.5
BG	NS	NS	5.0	5.7	5.2	5.2	5.4
Observer-rated signs (0–3)							
Good mood	4.20 (0.03)	NS	1.0	1.0	1.1	1.5	1.6
Stimulated	6.57 (0.0001)	2.08 (0.02)	0.0	0.0	0.4	0.8	0.8
Flushed face	3.89 (0.02)	NS	0.2	0.2	0.3	0.7	0.6
Sweaty	NS	NS	0.2	0.3	0.5	0.5	0.5
Nausea/vomiting	NS	NS	0.0	0.0	0.1	0.1	0.3
Red eyes	33.46 (0.0001)	1.77 (0.07)	0.0	0.0	0.4	1.3	1.8
Strength of effect	64.64 (0.0001)	NS	0.0	0.3	1.0	2.2	2.6

[a] The Time variable has nested within it two presmoking time points (pre- and post-naltrexone), four levels of the Marijuana Dose effect (zero, three, nine and 18 active puffs), and three postsmoking time points. The baseline (BL) mean given in this table is the average at the post-naltrexone time point.

[b] Degrees of freedom for plasma THC measure are (4,16) for Time and (8,32) for interaction terms.

[c] P-values appear in parentheses.

the reliability of this dose-effect did not significantly decrease using either finger alone compared with the average of the two latencies. Pearson correlations between mean finger withdrawal latencies and plasma THC (five time points) and HR (nine time points) were, $rs = 0.78$ and 0.75, respectively. Thus, there was good correspondence between indices of biological exposure and antinociception in the overall sample.

3.2.2. Biological exposure

Fig. 3 (upper panels) shows effects of marijuana smoking on biological exposure measures. Mean plasma levels of THC prior to smoking were 3 ng/ml, near the cut-off for detection. Immediately after smoking 0, 3, 9 and 18 cumulative active puffs (bouts 1–4), mean THC levels were 5, 161, 179 and 202 ng/ml, respectively. Plasma THC levels after 3, 9 and 18 active puffs did not significantly differ from one another, but all were significantly different than the presmoking and placebo smoking means. HR levels were stable prior to smoking, significantly increased upon smoking, and continued to increase through bout 4. CO increases occurred after each smoking bout (including placebo, as expected), whereas tachycardia resulted only when active doses (3, 9 and 18 puffs) were administered. Mean HR levels were very highly correlated with mean plasma THC levels (at the presmoking time point and just after each of the four marijuana doses), $r = 0.98$. After completion of smoking, HR levels returned to baseline more rapidly than CO levels.

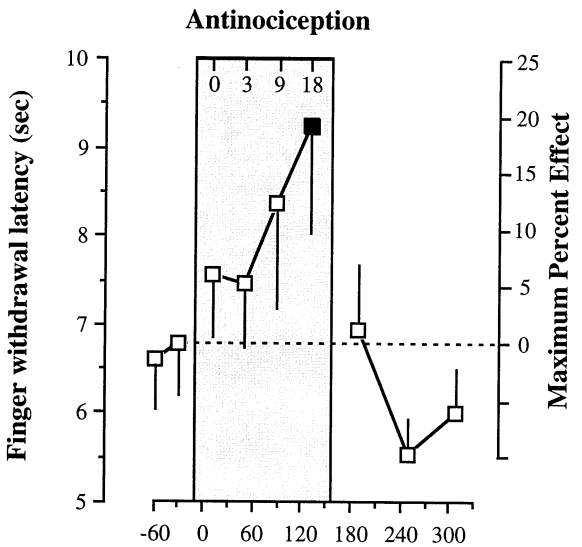

Fig. 2. Antinociceptive effects of cumulative marijuana smoking, as measured by finger withdrawal latency (in seconds, left axis) and maximum percent effect (MPE, right axis). The zero MPE is referenced to the pre-smoking control value (dashed line). Data in the shaded area indicate the 0-, 3-, 9- and 18-puff cumulative dose conditions (dose-effect curve). Data points to the left of the shaded area are presmoking and data points to the right are postsmoking. Dark icons indicate a significant difference from the placebo (zero-puff) condition. Means (with standard error bars) are collapsed across the three test sessions.

3.2.3. Psychomotor performance

As shown in Fig. 3 (lower left), marijuana produced dose-dependent decreases in gross motor stability (mean balance time); only the high dose condition significantly differed from the zero active-puff placebo condition. The magnitude of impairment at the high dose relative to control levels (45% decrease, from 29 to 16 s) was considerably greater than for the antinociception measure. Unlike finger withdrawal latency (which depends on a fine motor response), gross motor stability was still impaired at 1 h after smoking, and gradually returned to baseline.

On the DSST (Fig. 3, lower right), the number of attempts was stable across the two presmoking points and after the zero and three active-puff conditions. Subsequently, the number attempted significantly decreased, with even greater decrements at the 2-h postsmoking point. The number of correct responses showed an identical dose-dependent pattern (but slightly lower overall absolute scores) across assessment time points. Because of these parallel changes in the number of attempted and correct responses, the mean percentage of correct responses did not significantly vary as a function of dose (Table 1). Thus, marijuana smoking degraded performance speed but not accuracy on this psychomotor measure.

On the Divided Attention task, response latency (i.e. button-pressing reaction time to random visual targets) significantly differed over the time course of the session. Mean response latency was longest after 18 active puffs. However, this was not significantly different from placebo or presmoking levels due to large variability; rather, the time effect resulted from a difference between 18-puff and pre-naltrexone baseline time points. Accuracy in tracking (i.e. distance from) the visual targets was not significantly affected by marijuana dose.

Similar to the Divided Attention response latency measure, Digit Span measures (total correct and longest correct span) showed marginal session time effects, but interpretation of both effects was problematic due to performance variations in the control (presmoking and placebo) conditions.

3.2.4. Subjective effects

As expected, marijuana smoking produced significant, dose-dependent changes on the majority of subjective effects. Fig. 4 (upper left) illustrates mean VAS ratings of drug 'liking' and 'desire for more' (craving) marijuana before, during and after cumulative dose smoking. Relative to placebo, drug liking scores significantly increased after three active puffs, peaked after nine active puffs and were similarly elevated after 18 active puffs ($\approx$ 70% MPE). In contrast, mean ratings of desiring more marijuana peaked after only three active puffs and decreased at higher doses, thus demonstrating an inverted U-shaped (quadratic) dose-effect curve. The

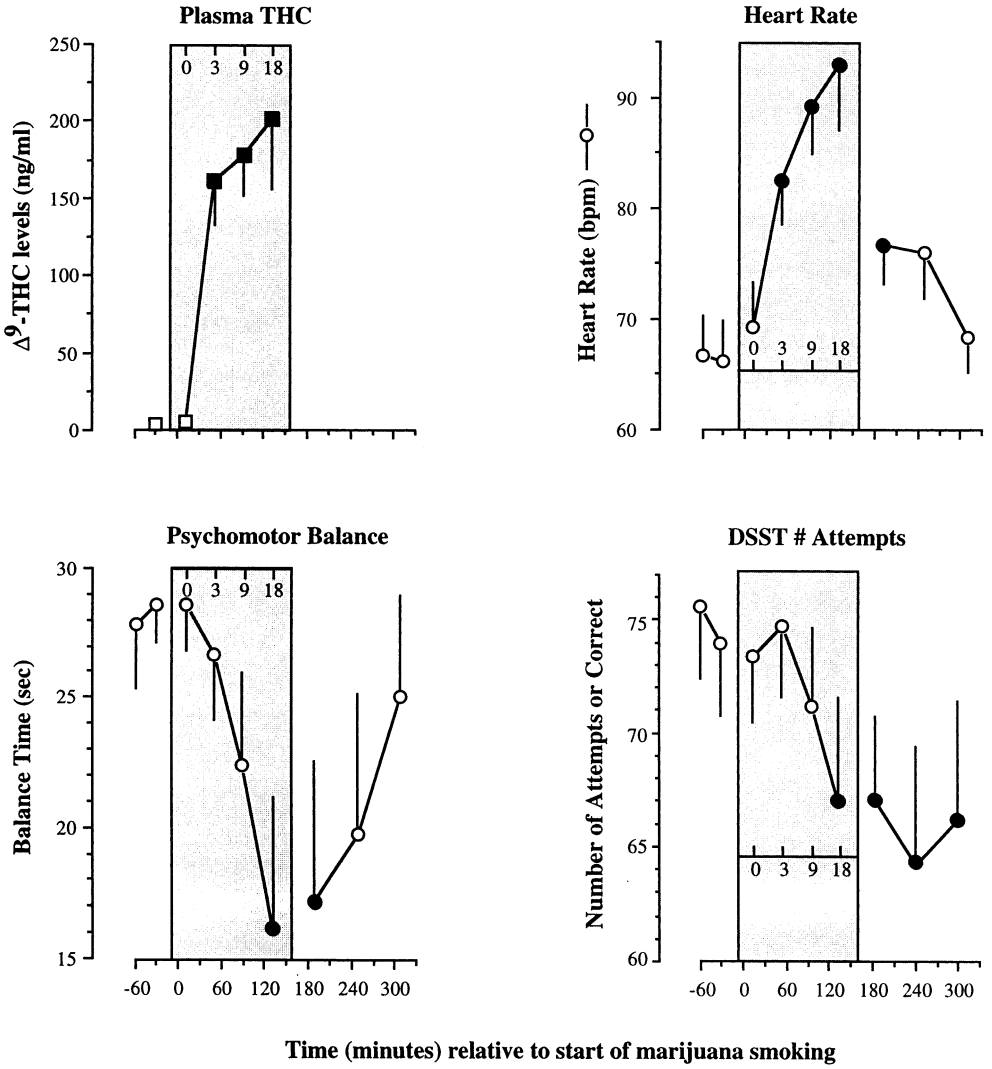

Fig. 3. Effects of cumulative marijuana smoking on biological exposure measures of plasma THC (upper left), HR levels (upper right), balance (lower left) and DSST performance (lower right). Data in the shaded area indicate the 0-, 3-, 9- and 18-puff cumulative dose conditions (dose-effect curve). Data points to the left of the shaded area are presmoking and data points to the right are postsmoking. Dark icons indicate a significant difference from the placebo (zero-puff) condition. Means (with standard error bars) are collapsed across the three test sessions.

contrast between these measures indicates a dissociation between liking the drug and wanting more of it.

Fig. 4 (upper right) demonstrates similarity between participants' comparison of drug effect strength (laboratory versus natural smoking) and reported value of (willingness to pay money for) the marijuana effect on the multiple choice form. The effect produced by smoking three puffs from 3.55% THC cigarettes was weaker than their usual marijuana smoking, whereas the effects produced after smoking nine and 18 puffs from these active cigarettes were stronger than their typical naturalistic experience. Marijuana monetary value exhibited dose-related increases, with the nine and 18 cumulative puffs showing equivalent, significant increases from the zero-puff control condition.

VAS ratings of any drug effect, high, good drug effect and stoned showed dose-dependent monotonic increases that were similar in magnitude (peaks in the 18 active-puff condition of $\sim$70 on the 0–100 scale) to that for the 'comparison' rating (Fig. 4, upper right and Table 1). Thus, the majority of typical marijuana subjective effects reached $\sim$70% of maximum under the dosing conditions studied here. VAS ratings of 'hungry' and 'impaired' showed dose-dependent monotonic increases but peaked at slightly lower levels in the 18-puff condition (Table 1). VAS ratings of 'bad drug effect', 'anxious' and 'confused' showed small mean increases that were greatest in the 18-puff condition at $\sim$10–20 on the 100-point scale. Although VAS ratings of 'sedated' and 'down' showed modest increases, these measures peaked (at $\sim$30 on the 100-point scale) during the postsmoking period.

Fig. 4 (lower left) illustrates results for two ARCI subscales, Marijuana and PCAG. Both exhibited dose-

dependent increases, but only the Marijuana scale scores showed a significant dose-effect during the smoking period. In contrast, PCAG (similar to the VAS 'sedated' rating) did not peak until the first postsmoking time point. MBG and AMPH subscale scores showed dose-related increases that peaked after nine active puffs, whereas LSD scores showed dose-related increases that peaked after 18 active puffs. Mean BG subscale scores did not significantly change during the session (Table 1).

3.2.5. Observer-rated signs

Of seven observer-rated signs, five (good mood, stimulated, flushed face, red eyes, and strength) showed significant dose-dependent effects of varying magnitude, whereas nausea/vomiting and sweaty did not (Table 1). The 'strength' measure, a composite score that was based on ratings of the other signs, was most sensitive to marijuana dose-effects (Fig. 4, lower right). Although there was a significant pretreatment × time interaction for 'stimulated', the marijuana dose-effect was not shifted by naltrexone in a dose-related manner.

4. Discussion

The goal of this study was to determine whether smoked marijuana produces dose-related antinociception in humans. The procedure used to test pain sensitivity (finger withdrawal from radiant heat) parallels the tail-flick assay often used in animals to demonstrate the antinociceptive effects of naturally-occurring and syn-

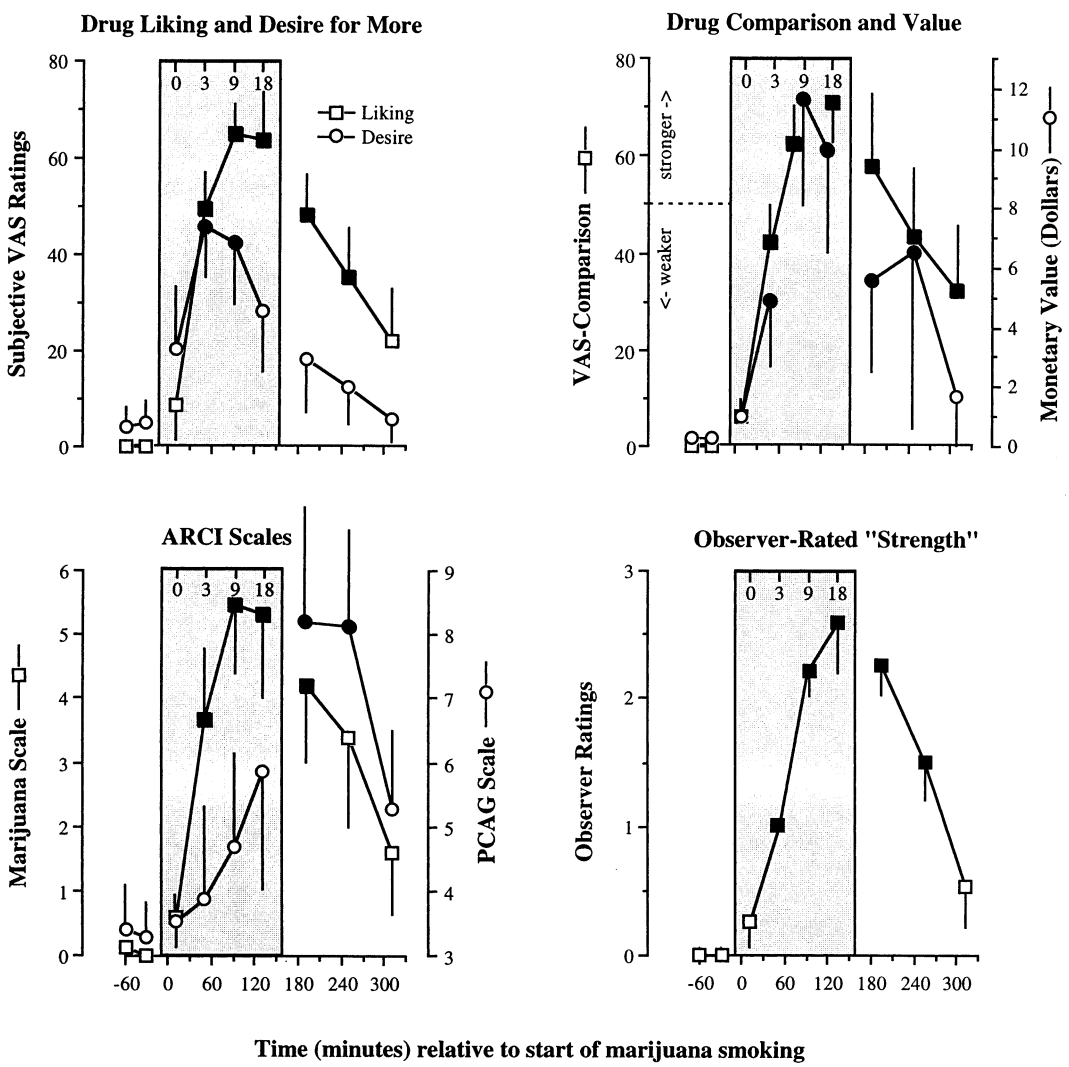

Fig. 4. Effects of cumulative marijuana smoking on subjective reports of drug liking and craving (upper left), drug comparison and monetary value (upper right), ARCI Marijuana and PCAG scales (lower left), and observer-rated behavioral signs (lower right). Data in the shaded area indicate the 0-, 3-, 9- and 18-puff cumulative dose conditions (dose-effect curve). Data points to the left of the shaded area are presmoking and data points to the right are postsmoking. Dark icons indicate a significant difference from the placebo (zero-puff) condition. Means (with standard error bars) are collapsed across the three test sessions.

thetic cannabinoid receptor ligands. A cumulative marijuana smoking procedure, extended from work by Chait et al. (1988), was used to evaluate this hypothesis and to efficiently collect a broad range of biobehavioral reference data. Higher doses were used in the present study (18 cumulative puffs, consumed in a standard manner over 2 h, from cigarettes containing 3.55% THC) than the Chait et al. study. This change anticipated the possibility that marijuana's antinociceptive potency or efficacy might be lower than for production of its biological (e.g. tachycardia), abuse-related (e.g. euphoric), and psychomotor-impairing effects. In addition, we tested the hypothesis that the endogenous opiate system might modulate cannabinoid effects in humans by administering the opioid antagonist naltrexone (0, 50 and 200 mg p.o.) acutely prior to three, otherwise identical, smoking sessions.

Marijuana smoking produced a dose-dependent increase in antinociception. The linear increase in pain threshold was only significant at the highest dose. Antinociception was relatively weak (19% MPE) in this assay. In contrast, tail-flick studies in rats and mice have shown that systemically administered THC (which is the best available comparison to human marijuana smoking) is a more effective ($>80\%$ MPE) antinociceptive agent (Lichtman and Martin, 1991; Welch, 1993a; Lichtman and Martin, 1997) than observed here. However, the present data are concordant with results of a study with rhesus monkeys using the warm water tail-withdrawal assay (Vivian et al., 1998). Whereas heroin and the kappa opioid agonist U-69593 completely blocked the tail-withdrawal response in 50 and 55°C water (100% MPE), a cumulative dose of 3.2 mg/kg i.m. THC produced more limited antinociception ($\approx$ 70% MPE) in 50°C water and only 15% MPE in 55°C water. Thus, both data in non-human primates and humans are consistent in showing that systemically administered THC produces limited-efficacy thermal antinociception.

Caution is warranted when comparing the present results to animal data. First, the marijuana plant contains multiple cannabinoids that may potentiate or reduce THC-induced antinociception. For example, cannabidiol antagonized THC antinociceptive activity in mice (Wellburn et al., 1976) and cannabinol antagonized THC-induced tachycardia in humans (Karniol et al., 1975). Second, THC doses are not comparable across species; as a result, THC doses of 3.2 mg/kg or more in animals may appear to be more effective than the limited doses that can be administered to humans. Third, the withdrawal latency cut-off time of 20 s in the present study is longer than typically used with rats and mice (≤ 10 s) although identical to the primate study by Vivian et al. (1998). In the present study, no latency on any test trial exceeded the 20-s criterion (range, 3.9–16.6 s). This higher cut-off value therefore underestimates marijuana's MPE relative to animal studies. Fourth, compared with the present study, the shorter latencies obtained in animal studies probably reflect the use of a higher-intensity radiant heat stimulus. In contrast, we deliberately used a lower-intensity stimulus (i.e. trained a baseline latency that was 6–8 s), customized for each participant, so that a weak antinociceptive effect of marijuana might be more detectable. Finally, all participants in the present study were relatively frequent marijuana users; this may have led to greater tolerance to the antinociceptive effects of marijuana smoking. It is clear that tolerance and cross-tolerance develops to cannabinoid antinociception in animals (Fan et al., 1994). Perhaps greater effects may have been observed if marijuana-naïve or infrequent marijuana users had served as participants.

Marijuana doses in the present study produced significant changes on other biological, abuse- and impairment-related reference measures. Therefore, it might be inferred that marijuana is a less effective (i.e. partial agonist) or less potent antinociceptive agent relative to its ability to produce these other effects and, in turn, has a limited therapeutic margin for analgesia. Although we chose a thermal assay similar to the animal tail-flick test for this demonstration, marijuana's antinociceptive effects in humans might be greater in a different assay condition, e.g. an inflammatory pain model (cf. Smith et al., 1998). Interestingly, the non-steroidal anti-inflammatory drug indomethacin antagonized certain of marijuana's effects in one human study (Perez-Reyes et al., 1991); whether a similar effect might occur with antinociception has not been evaluated.

One alternative explanation for the antinociceptive effect is that marijuana produced motor slowing, thereby increasing finger withdrawal latencies at higher doses. However, other measures of psychomotor function discount this possibility. First, Divided Attention visual target response latency is topographically similar to finger withdrawal; however, this measure was not significantly affected by marijuana dose. These data are consistent with conclusions from a review by Chait and Pierri (1992), indicating only weak effects of marijuana on simple reaction time. Second, although balance was reduced in a dose-dependent manner, this measure of gross motor stability differs from the fine-motor withdrawal response to acute heat stimulation. Further, the duration of balance impairment was longer than that observed for finger withdrawal latency. Third, DSST motor speed (but not accuracy) decreased as a function of marijuana dose. Like balance, DSST impairment and finger withdrawal latency changes exhibited different time courses. Finally, the ARCI PCAG scale (a sedation measure correlated with motor impairment) increased before peak antinociception but, like disruption of motor balance, continued at the same level for

2 h after smoking ended. Thus, it appears unlikely that a general motor disturbance or sedation accounts for the increased finger withdrawal latency produced by higher doses of marijuana.

Another explanation for increasing withdrawal latency is that marijuana smoking produced peripheral hypothermia (decreased finger temperature), making participants less sensitive to radiant heat stimulation. Consequently, finger withdrawal latency increases might be mediated by THC-induced changes in vasomotor tone rather than CNS factors. Marijuana produces hypothermia in animals (Dewey, 1986; Adams and Martin, 1996), and some authors have argued that any drug which produces hypothermia may increase tail-flick latency (Berge et al., 1988; Tjolsen et al., 1989; Hole et al., 1990; Han and Ren, 1991). Because this hypothesis is based on correlational evidence, Lichtman et al. (1993) directly manipulated drug (including THC) and non-drug variables (e.g. heat intensity) to determine the relationship between tail-skin temperature and tail-flick latency. They concluded that there was a negligible relationship between temperature and response latency, and that it was unnecessary to control this variable. Despite this empirical evidence in animals, the role of hypothermia in the present data set cannot be excluded because this factor has not been systematically evaluated in humans.

The present study extends observations of Chait et al. (1988) regarding dose-effects of smoked marijuana. The procedure used here resulted in different dose deliveries from the Chait et al. study. First, participants in the present study smoked more puffs from more potent cigarettes but at less frequent intervals. Second, Chait et al. cut cigarettes in half prior to smoking whereas in the present study they were not. This is important because more THC is delivered in the proximal than distal fraction of the cigarette during pyrolysis (Tashkin et al., 1991). Third, although interpuff interval and breathhold duration parameters were similar across studies, Chait et al. (1988) did not control puff volume or inhalation volume whereas these factors were controlled here. Fourth, unlike Chait et al. we did not include a placebo smoking session (which would control for time and puff inhalation effects). Although this is a possible limitation of the present study, data from Chait et al. and our own data (Greenwald and Stitzer, 1994) indicate negligible effects of placebo marijuana smoking. Despite these procedural differences, the two studies produced remarkably consistent findings.

Although plasma THC levels were not measured by Chait et al. (1988) it is feasible to compare studies using HR changes, which are sensitive to marijuana dose (Chait and Pierri, 1992). In this study, plasma THC and HR means were highly correlated across assessment time points. Although baseline HR levels differed between studies, there was about a 10-bpm greater HR increase in the present study after each active smoking bout compared with the Chait et al. study. This indicates that the present smoking parameters produced greater overall biological exposure, but the studies did not differ in within-session tolerance to THC-induced tachycardia. At comparable doses, there was a similar degree of change observed on identical subjective effects (ARCI Marijuana scale and 'high' and 'hungry' VAS ratings) across the two studies, but effects on identical psychomotor measures (Digit Span and Divided Attention) were less statistically robust in the present study. Qualitatively, the strength of the marijuana effect in the present study led to substantial attrition of participants. This may have influenced estimation of effect size for some measures in the present study; however, it actually reinforces the conclusion that marijuana-induced antinociception is rather weak relative to the other biobehavioral reference measures.

One advantage of the cumulative dosing paradigm is that it can be used to study effects of drug pretreatments. This permits analysis of the neuropharmacological mechanisms of marijuana actions in humans and, ultimately, screening pharmacological agents for treating marijuana abuse and dependence. In contrast to animal studies that showed partial attenuation of THC antinociception with systemically administered opioid antagonists (Wilson and May, 1975; Tulunay et al., 1981; Ferri et al., 1986), the high doses of naltrexone used in this study did not influence marijuana-induced antinociception. On the other hand, the results are consistent with recent evidence that systemic administration of the opioid antagonist quadazocine does not attenuate THC antinociception (Vivian et al., 1998). There may be several reasons for this lack of effect. First, marijuana (or THC) may primarily produce antinociceptive effects in humans through cannabinoid receptors. If so, only a cannabinoid antagonist would be expected to attenuate such effects. Second, naltrexone may not sufficiently penetrate the spinal cord and/or stimulate spinal kappa opioid receptors. In healthy humans, 50 mg naltrexone saturates brain mu-opiate receptors (Lee et al., 1988); however, the ability of naltrexone to bind to kappa-receptors in human brain and spinal cord is unknown. Some previous animal studies found that only i.t. naltrexone attenuated THC antinociception (Welch, 1993a,b; Smith et al., 1994). Third, there may be species differences, e.g. THC antinociception via spinal kappa receptors may be specific to rodents and not humans. To resolve some of these issues, it would be desirable to administer a cannabinoid antagonist or a kappa-opioid antagonist (which were unavailable for human use when this study was conducted) prior to cumulative marijuana smoking. Finally, the present data are internally consistent, in

that naltrexone also did not influence marijuana dose-dependent changes on biobehavioral measures. The absence of a naltrexone effect is consistent with previous animal studies that have shown opioid antagonists do not alter THC discriminative stimulus effects (Järbe and Ohlin, 1977; Browne and Weissman, 1981).

Cumulative dosing procedures can be used to compare indices of marijuana effect that exhibit dose-proportionality versus those that show less than proportional dose-effects. Depending on the doses and intervals (i.e. interpuff and interbout) selected, greater or lesser effects could develop relative to a single-dose procedure. Under the conditions of this study, few measures showed dose-proportional changes (e.g. balance). Rather, most measures exhibited mean changes that were either linear but less than dose-proportional (e.g. antinociception, plasma THC, HR, drug comparison VAS, observer ratings), reached a plateau (e.g. drug liking, ARCI Marijuana scale), or showed an inverted U-shaped function (e.g. desire for more drug, monetary value). Whether these differential changes are due to dispositional, pharmacodynamic or behavioral tolerance is not presently clear. It should be noted that THC plasma levels did not significantly differ between the 3, 9 and 18 puff conditions (but did differ from placebo) in this study. This lack of separation between active doses probably reflects the longer interbout interval used and rapid decreases in blood levels typically observed after marijuana smoking.

The antinociception data reported here are potentially relevant to the ongoing debate concerning therapeutic use of cannabinoids for analgesia (Gurley et al., 1998; Marmor, 1998; Smith, 1998; Taylor, 1998). A crucial caveat is that the present data were collected with healthy, regular marijuana users who smoked acute doses in a controlled laboratory situation and were exposed to a thermal stimulus. Although it is not possible to predict whether chronically ill patients taking cannabinoids for pain relief would respond similarly, the present data are consistent with previous studies (Noyes et al., 1975, 1976) showing that THC-induced analgesia was accompanied (and outlasted) by side-effects such as sedation. These results indicate that, at doses producing substantial biological exposure, the antinociceptive effects of marijuana — although statistically significant — were rather weak ($\approx$20% MPE) compared with motor-impairing and subjective effects (45–70% MPE). Further, reduction in pain sensitivity recovered rapidly (within 1 h) whereas the physiological, subjective and performance effects persisted long after smoking. Although these results should be cautiously interpreted, they suggest that the antinociceptive efficacy of marijuana in a human laboratory setting is probably marginal in relation to its other biological, abuse-related, and performance-impairing effects.

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