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Lack of Analgesia by Oral Standardized Cannabis Extract on Acute Inflammatory Pain and Hyperalgesia in Volunteers

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Background: **Cannabinoid-induced analgesia was shown in animal studies of acute inflammatory and neuropathic pain. In humans, controlled clinical trials with Δ^9-tetrahydrocannabinol or other cannabinoids demonstrated analgesic efficacy in chronic pain syndromes, whereas the data in acute pain were less conclusive. Therefore, the aim of this study was to investigate the effects of oral cannabis extract in two different human models of acute inflammatory pain and hyperalgesia.**

Methods: **The authors conducted a double-blind, crossover study in 18 healthy female volunteers. Capsules containing Δ^9-tetrahydrocannabinol–standardized cannabis extract or active placebo were orally administered. A circular sunburn spot was induced at one upper leg. Heat and electrical pain thresholds were determined at the erythema, the area of secondary hyperalgesia, and the contralateral leg. Intradermal capsaicin-evoked pain and areas of flare and secondary hyperalgesia were measured. Primary outcome parameters were heat pain thresholds in the sunburn erythema and the capsaicin-evoked area of secondary hyperalgesia. Secondary measures were electrical pain thresholds, sunburn-induced secondary hyperalgesia, and capsaicin-induced pain.**

Results: **Cannabis extract did not affect heat pain thresholds in the sunburn model. Electrical thresholds (250 Hz) were significantly lower compared with baseline and placebo. In the capsaicin model, the area of secondary hyperalgesia, flare, and spontaneous pain were not altered.**

Conclusion: **To conclude, no analgesic or antihyperalgesic activity of cannabis extract was found in the experiments. Moreover, the results even point to the development of a hyperalgesic state under cannabinoids. Together with previous data, the current results suggest that cannabinoids are not effective analgesics for the treatment of acute nociceptive pain in humans.**

THE detection of two specific cannabinoid receptors (CB_1 and CB_2) and their endogenous ligands prepared the ground for numerous animal studies with different cannabinoids, confirming analgesic, antihyperalgesic, and antiinflammatory activities of exogenous and endogenous ligands[1–5] in these models. However, inconsistent data exist from the few controlled clinical studies on the potential analgesic effect of oral cannabinoids such as Δ^9-tetrahydrocannabinol (THC).[6–8] No analgesic effect was found after a postoperative oral dose of 5 mg THC, whereas significant dose-related reductions of analgesic rescue medication by a single dose of 10 or 15 mg THC were demonstrated in a recent study with oral THC-standardized cannabis extract.[9,10]

Using purely nociceptive stimuli in an experimental setting, a recent trial did not show any analgesic effect of 20 mg oral THC.[11] However, the stimuli used in those experiments may be considered inappropriate to find any antineuropathic or antihyperalgesic drug effects. In contrast, the prevention of capsaicin-induced pain was reported using a model of topical administration of the synthetic cannabinoid HU-210 onto human skin.[12]

Besides studies with smoked cannabis,[13,14] no controlled experimental clinical trials on the analgesic efficacy of oral cannabis extract or THC on acute inflammatory pain and hyperalgesia in humans have been published to date. Therefore, the current study was designed to detect a potential analgesic activity of oral THC-standardized cannabis extract by two different and well-established human models of acute inflammatory pain and hyperalgesia, *i.e.*, the sunburn model and the intradermal injection of capsaicin.

Materials and Methods

Study Population and Design

After institutional review board (Ethics Committee of the Medical University of Vienna, Vienna, Austria) approval and written informed consent, 18 healthy female volunteers without a history of cannabis use participated in this randomized, double-blind, active placebo–controlled, crossover study. Only female volunteers were included, because animal studies suggested a more pronounced effect of cannabinoids in females compared with males.[15,16] After completion of a confidential medical questionnaire and a physical examination (including electrocardiography, blood pressure, body temperature, and standard chemical blood test), the Mini-International Neuropsychiatric Interview (M.I.N.I. German Version 5.0.0) and a structured face-to-face psychiatric interview were used to exclude any psychiatric disorder.

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General exclusion criteria were a history of or any existing drug abuse (urine multidrug screening test; Coachrom Diagnostics, Vienna, Austria); psychiatric disorder; smoking (> 5 cigarettes/day); drug treatment except contraceptives in the past 14 days; pregnancy (urine test before each treatment); infections; liver, renal, cardiac, or skin diseases; and current acute or chronic pain conditions.

The volunteers agreed to abstain from alcohol, nicotine, and caffeinated drinks for 24 h before and during the study sessions, and also from oral food intake for 12 h before the session.

Experimental Conditions and Monitoring

The study sessions were always performed in the same quiet and air-conditioned room at 22°C environmental temperature, starting at 8:00 AM. The same two trained investigators performed all tests, which started with a short physical examination, urine pregnancy test, and drug screening. A venous cannula was placed into a cubital vein, and the monitoring of blood pressure, electrocardiography, body temperature, and pulse oximetry was established before the individual baseline pain thresholds were determined. The expected typical side effects of drowsiness, euphoria, sedation, nausea, dry mouth, and vertigo were evaluated every hour by the subject herself and by the blinded investigator, using a visual analog scale (VAS). To detect acute psychotic symptoms, the psychiatric status was assessed with the validated Brief Psychiatric Rating Scale, consisting of 18 items rated on seven-point severity scales before and 3 and 6 h after the intake of cannabis extract or placebo.[17]

Pain measurements were performed after defined time intervals in a uniform sequence: reaction time, pinprick, heat pain perception and tolerance, and electrical pain perception and tolerance. All sessions started 20 ± 0.5 h after ultraviolet-B irradiation, and the test battery was repeated exactly 2 h after oral intake of study medication (fig. 1). Each subject remained hospitalized in our pain center for 8 h after drug administration. The washout period between the two respective crossover test sessions was at least 4 weeks.

Study Medication

After baseline measurements, each proband received four indistinguishable brown and one white capsule containing either standardized cannabis extract calibrated on a THC content of 20 mg in total (Institute for Clinical Research, Berlin, Germany) or active placebo (5 mg diazepam; Nycomed, Linz, Austria), in a double dummy design together with a standardized breakfast (herbal tea or decaffeinated coffee, small breads with hazelnut cream [Nutella®; Ferrero Inc., Innsbruck, Austria]). The cannabis extract was a product of pharmaceutical quality containing a mixture of cannabinoid plant extracts in a gelatin base, provided by the Institute for Clinical Research that had been used already in previous studies.[10,18] THC and cannabidiol (CBD) predominated and

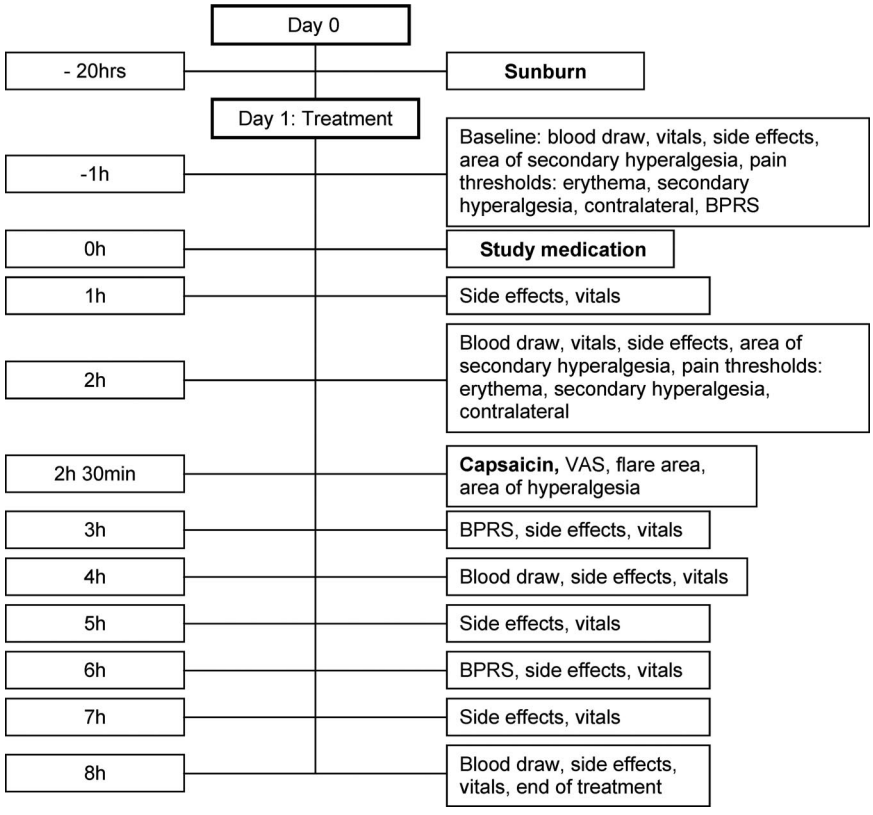

Fig. 1. Time schedule of study-related actions. BPRS = Brief Psychiatric Rating Scale; VAS = visual analog scale for pain intensity (0–10).

were in the ratio of 2:1; other plant cannabinoids were less than 5% per capsule.

The blinding of the study medication was performed by our hospital pharmacy according to a computerized randomization list. To verify a sufficient gastrointestinal absorption and bioavailability, plasma levels of THC, CBD, and the two THC-metabolites 11-hydroxy-THC (THC-OH) and 11-nor-9-carboxy-THC (THC-COOH) were determined before and 2, 4, and 8 h after administration of the study medication. The heparinized blood samples were instantly centrifuged, and the plasma was frozen and stored at −20°C until analysis. Cannabinoids were analyzed by gas chromatography–mass spectrometry at the Department of Legal Medicine, University Hospital Charité, Berlin, Germany.[19]

Experimentally Induced Pain and Hyperalgesia

Sunburn Model. Ultraviolet B–induced inflammation of the skin is an established model of hyperalgesia in humans. In this model, primary and secondary hyperalgesia are considered to reflect peripheral and central mechanisms of pain, respectively.[20]

As previously described,[21] 20 h before each treatment session, a circular spot (diameter 50 mm) was irradiated with the threefold individually determined minimal erythema dose at one upper leg using a calibrated ultraviolet-B source (Sellasol; Sellas Medizinische Geraete GmbH, Gevelsberg-Vogelsang, Germany; wavelength 290–320 nm). According to the crossover design, one leg was irradiated for each session, and the side of first irradiation was randomized. The irradiation procedure induced a state of local hyperalgesia that remained constant between 20 and 30 h thereafter.[20]

Before the measurements of baseline pain thresholds, the area of secondary hyperalgesia surrounding the erythema was determined by pricking with a von Frey filament (150 g) and by brush stimulation, while the probands kept their eyes closed. Stimulation was started 100 mm distant from the central erythema and was repeated along a pattern of eight radial spokes. While moving along each spoke in 5-mm intervals, the subject was asked to report when the sensation of the pricking changed definitely. The borders were marked with a pen, and the respective distance to the erythema was measured. Subsequently, marks were erased to avoid any bias during the following measurements. The area of pinprick hyperalgesia was calculated as an octagon based on the eight obtained radial distances.

Intradermal Capsaicin Model. Intracutaneous administration of capsaicin is an established model to induce spontaneous pain, followed by secondary mechanical hyperalgesia and neurogenic flare reaction.[22–24] Because of the release of neuropeptides by nociceptors, capsaicin leads to a rapid onset neurogenic inflammation. The immediate strong pain after capsaicin injection is followed by a secondary (mechanical) hyperalgesia that involves central sensitization rather than sensitization of peripheral nociceptors and is therefore considered a model of secondary hyperalgesia.

During every session, exactly 2.5 h after medication, 20 μl capsaicin, 0.1% (vol/vol), was injected intradermally into a defined test area on one forearm contralaterally to the sunburn site. Pain intensity was rated by VAS at 15-s intervals for the first 2 min, followed by measurements at 2.5, 9, and 15 min after the injection. The flare area was assessed by tracing the edge of the visible erythema on a transparent acetate sheet 10 min after injection. The area was calculated using the software Osiris 4.19 for Microsoft Windows (University of Geneva, Geneva, Switzerland). The hyperalgesic area was determined by pinprick and brush stimulation along six radial spokes (see Sunburn Model section).

Pain Measurements

Training Phase. To make all of the subjects equally familiar with the test procedures, a preceding training session was always performed when the subjects presented for the ultraviolet-B irradiation 1 day before the actual drug treatment session.

Heat Pain Thresholds. Heat pain perception (HPPT) and tolerance (HPTT) thresholds were assessed by a thermal sensory testing device (TSA-2001; Medoc, Ramat Yishai, Israel) and always performed in a uniform sequence at three different sites: contralateral leg, area of secondary hyperalgesia, and sunburn erythema. A Peltier thermode, size 18 × 18 mm, was attached to the skin at the sites of measurement using an elastic bandage. The bandage was wrapped tightly around the upper leg, stretched by 2 cm, and the ends were fixed. Much care was taken to consider upper leg curvatures in placing the probe to achieve optimal skin contact. Skin adaptation temperature was 32°C, and the rate of temperature change was 0.8°C/s (heat ramp) with a return rate of 4°C/s. The stimulator temperature span ranged from 32° to 54°C. HPPT and HPTT were measured with the method of limits as previously described.[25] The trained subject was instructed to stop the increase in heat immediately when the stimulus became painful. The measurements of the HPPT were repeated three times and averaged. To determine the HPTT, the subject was advised to stop the increase of heat as soon as the painful stimulus became intolerable. This test was repeated twice and averaged. A 60-s interstimulus resting period separated the heat pain threshold determinations.

Electrical Pain Thresholds. Electrical pain perception (EPPT) and tolerance (EPTT) thresholds were determined using an automated electric current sensory testing device (Neurometer® CPT/C; Neurotron Inc., Baltimore, MD). A pair of 10-mm-diameter gold electrodes separated by a 17-mm Mylar spreader was coated with a thin layer of chloride-free electroconductive gel and taped onto the skin of the three consecutive testing sites. The pain

thresholds for two different frequencies (5 Hz, 250 Hz) of a constant current sine wave stimulus were tested. EPTT determinations were performed using a standardized automated double-blinded methodology. The stimulus was presented in an ascending staircase fashion from zero to a maximum of 9.99 mA. The duration of each step was a function of the stimulus frequency: 2.52 s at 5 Hz (29 steps) and 2.16 s at 250 Hz (20 steps).The electrical pain thresholds were determined by the subject pressing and holding the "Test Cycle" button. The subjects were instructed to discontinue the increase in stimulus intensity when the stimulus became painful (EPPT). The tests were repeated three times and averaged. To determine the EPTT, the subjects were asked to stop the increase of the stimulus intensity immediately when the stimulus became intolerable. This test was repeated twice and averaged. There was a 60-s interstimulus resting period between each threshold measurement. For safety reasons, the stimulation automatically stopped at the maximum output intensity (9.99 mA).

Reaction Time. At baseline and 2 h after medication, the individual's reaction time was assessed by pressing the button of a stopwatch initialized together with an acoustic signal. Subjects were asked to stop the watch as fast as possible when the signal appeared in intervals of 5–15 s in random order. Measurements were repeated three times and averaged.

Statistical Analysis

The biometrical analysis was performed at the Institute for Clinical Research, Berlin, with the exception of the Brief Psychiatric Rating Scale scores, which were analyzed at the Department of Biologic Psychiatry with SPSS for Windows, version 11.0 (SPSS Inc., Munich, Germany).

In previous studies,[21,25] an SD of the threshold difference between 2 study days of 0.42°C and 2,107 mm^2 for HPTT and area of secondary hyperalgesia were observed, respectively. To detect a 0.5°C reduction of HPTT in the sunburn with 80% power in the crossover design, a sample size of 2×4 (4 patients in each sequence) suffices, assuming a two-sided significance level of 5%. A 30% reduction of secondary hyperalgesia area can be detected with 2×6 probands.

Statistics were calculated with the software SAS® version 8.2 (SAS Inc., Cary, NC). The intention-to-treat analysis set used for efficacy analysis was defined as all subjects who finished at least one study period and provided at least one measurement on outcome for the second period. Thereby, missing observations were replaced using the last observation carried forward principle. Safety data were analyzed from all subjects enrolled.

All efficacy parameters were regarded as interval scaled and were analyzed using mixed linear models,[26,27] including the parameters "treatment" and "period" as fixed factors, the parameter "general reactivity" as continuous covariate, and each individual study subject as random factor. Dependent variables were chosen as changes from baseline, except for the flare area where no baseline measurements were taken. Carryover effects were not included because they were considered to be negligible due to the 4-week washout phase between the treatment periods. The model estimates for the fixed effects and for the continuous covariate were tested for significance by *t* tests on a two-sided α error level of 5%.

In total, for the primary analysis of efficacy five separate measurements were combined to two efficacy indices. The parameters "heat pain threshold at erythema site" (averaged from three consecutive measurements) and "heat pain tolerance at erythema site" (averaged from two consecutive measurements) were joined to a global index "primary hyperalgesia" by summing up the respective standardized changes from baseline.

For the second primary efficacy parameter, another global index, called "secondary hyperalgesia," was calculated by summing up the standardized changes from baseline with regard to the parameters "area of secondary hyperalgesia" (averaged from two assays using pinprick and brush) and "heat pain perception threshold" (averaged from two consecutive measurements).

The primary analysis of efficacy was performed in the *a priori* fixed order "primary hyperalgesia–secondary hyperalgesia," thus keeping the global α error.

Regarding the secondary analysis of efficacy as well as the analysis of safety, the same statistical model was used. For adverse events, incidence rates were calculated and compared between treatment groups by χ^2 test. All tests comparing those parameters between active drug and placebo are reported with their local *P* values (*i.e.*, without adjusting for multiple testing), serving as flags for differences that would be statistically significant ($P < 0.05$) if chosen as primary efficacy criterion.

Results

Demographic Data

All randomized female subjects could be included in the intention-to-treat analysis set. Therefore, intention-to-treat and safety sets were identical (table 1).

Cannabinoid Plasma Levels

Cannabinoid plasma levels were measured at 2, 4, and 8 h after drug intake. Despite the standardized conditions, a broad variability in peak plasma levels for all cannabinoids was observed, ranging between 1.05 and 7.92 ng/ml (mean ± SD, 4.23 ± 2.28 ng/ml) for THC and 0.46 and 3.57 ng/ml (1.71 ± 1.00 ng/ml) for CBD. Peak plasma levels were found between 2 and 4 h, coinciding with the time when pain measurements were performed. At 2 h, mean metabolite levels for THC-11-OH were 6.28 ±

Table 1. Demographic Data

Age, yr	23.45 ± 2.6
Systolic blood pressure, mmHg	118.50 ± 9.5
Diastolic blood pressure, mmHg	74.50 ± 11.0
Heart rate, beats/min	77.50 ± 12.0
Body temperature, °C	36.50 ± 0.35
Weight, kg	61.80 ± 8.40
Body height, cm	168.00 ± 6.0
Body mass index, kg/m^2	21.60 ± 2.35

Median values ± SDs of the 18 healthy female subjects who were included in the study after screening.

3.20 and 37.95 ± 21.48 ng/ml for THC-COOH. There was no correlation between individual plasma levels of THC, CBD, metabolites, and pain thresholds.

Side Effects

The applied dose of cannabis extract did not significantly affect systolic and diastolic blood pressure, oxygen saturation, or body temperature. Only the mean heart rate was significantly elevated compared with baseline or placebo, but returned to normal until the end of the study session. The heart rates reached their maximum approximately 3 h after administration of the study medication, correlating also with the painful injection of capsaicin.

Psychotropic and other side effects were stronger and more frequent after cannabis extract than after placebo (table 2). The intensity of each side effect was independently rated by a VAS before (baseline) and at every hour after the study medication by both the subject and the blinded investigator. Ratings reached their maximum between 2.2 and 3.2 h after drug administration and returned to baseline within 8 h. No correlation between the intensity of side effects and changes of heart rate and blood pressure was found.

To detect acute drug-induced psychotic symptoms, the psychiatric status was assessed by the means of the Brief Psychiatric Rating Scale scores at baseline and 3 and 6 h after the intake of the study medication. Despite the obligatory psychiatric prescreening, one subject experienced acute psychotic symptoms (total score, 84) after cannabis extract, such as unpleasant depersonalization, suspicion, derealization, and anxiety for approximately 4 h. During this period, pain measurements according to the study protocol could not be performed, and she was not included into the statistical analysis. The symptoms attenuated in the course of time and completely disappeared within the observation period of 8 h.

Table 2. Side Effects

	Self-rated VAS		Observer VAS	
Side Effect	Cannabis	Placebo	Cannabis	Placebo
Drowsiness	57.3 ± 20.8*	33.6 ± 23.4	67.2 ± 16.9*	40.4 ± 20.2
Sedation	79.1 ± 17.2*	12.2 ± 18.4	59.9 ± 26.5*	9.5 ± 11.2
Euphoria	38.2 ± 35.7	1.0 ± 0.8	25.3 ± 23.3	1.9 ± 4.7
Nausea	27.7 ± 30.5	1.6 ± 2.8	20.5 ± 30.3	0.8 ± 1.0
Dry mouth	70.9 ± 23.9*	4.5 ± 6.1	47.9 ± 27.9*	3.6 ± 4.3
Vertigo	65.0 ± 32.3*	2.3 ± 3.0	48.8 ± 31.8*	2.0 ± 4.2

Data are presented as mean (difference from baseline) ± SD for the whole 8-h study period (n = 17).

* $P < 0.05$.

Placebo = 5 mg diazepam; VAS = visual analog scale (0–100).

Sunburn Pain Model

Contralateral Pain Measurements. Heat pain thresholds (HPPT, HPTT), electrical pain thresholds (EPPT, EPTT), and pinprick pain (VAS) were measured first at the contralateral leg, in normal nonsensitized skin. For all parameters, no significant analgesic effect of cannabis extract or placebo could be found. Electrical pain thresholds were even diminished, showing an unexpected tendency toward hyperalgesia, without reaching statistical significance, however (table 3).

Secondary Hyperalgesia. The sunburn erythema was surrounded by the area of secondary hyperalgesia, which was assessed before and 2 h after the study medication. The extent of the area of secondary hyperalgesia was not altered by cannabis extract or placebo (data not shown) for both pinprick and brush stimuli. There was no difference in HPPT and HPTT between baseline, cannabis extract, and placebo (fig. 2).

EPPT and EPTT (5 and 250 Hz) were also determined in the area of secondary hyperalgesia. Compared with healthy skin, all pain thresholds were decreased. However, similar to the results obtained for normal skin, EPPT and EPTT were lower after cannabis compared with baseline and placebo, but again without reaching statistical significance (table 4).

Primary Hyperalgesia (Sunburn Erythema). Within the erythema site, neither cannabis extract nor placebo had any significant effect on HPPT or HPTT (fig. 3). Also, cannabis extract did not alter pinprick pain in the inflamed skin area. Surprisingly, the electrical pain thresholds EPPT and EPTT for 250 Hz were significantly decreased after cannabis extract (fig. 4).

Table 3. Contralateral Pain Measurements (Normal Skin)

Parameter	Baseline	Cannabis	Placebo
HPPT, °C	42.5 ± 4.0	42.3 ± 4.0	43.2 ± 2.8
HPTT, °C	48.3 ± 2.1	47.9 ± 2.2	48.3 ± 1.5
EPPT 5 Hz, mA	0.843 ± 0.46	0.789 ± 0.68	0.670 ± 0.64
EPTT 5 Hz, mA	2.406 ± 1.41	1.583 ± 0.99	1.615 ± 1.29
EPPT 250 Hz, mA	1.597 ± 1.77	1.180 ± 1.11	1.086 ± 0.99
EPTT 250 Hz, mA	3.488 ± 2.49	2.668 ± 1.91	2.897 ± 2.31
Pinprick VAS	19 ± 12	22 ± 15	17 ± 12

Data are presented as mean ± SD (n = 17) of the pain measurements at the contralateral leg. Electrical pain thresholds were insignificantly lower after cannabis compared with placebo (5 mg diazepam) ($P > 0.05$).

EPPT = electrical pain perception threshold; EPTT = electrical pain tolerance threshold; HPPT = heat pain perception threshold; HPTT = heat pain tolerance threshold; VAS = visual analog scale.

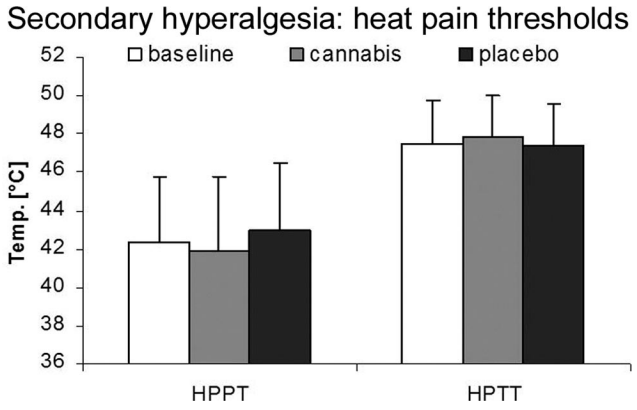

Fig. 2. Effect of cannabis extract on heat pain perception threshold (HPPT) and heat pain tolerance threshold (HPTT) in the area of secondary hyperalgesia surrounding the sunburn erythema. Data are presented as mean ± SD of the temperature when further warming was stopped by the subject before and 2 h after drug administration (n = 17). No significant differences between baseline, cannabis extract, and placebo (diazepam) ($P > 0.05$) were observed.

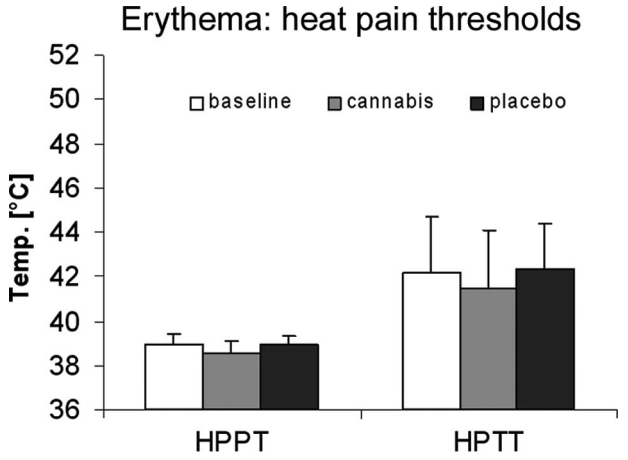

Fig. 3. Effect of cannabis on heat pain perception threshold (HPPT) and heat pain tolerance threshold (HPTT) in the area of primary hyperalgesia (erythema). Data are presented as mean ± SD of the temperature when further warming was stopped by the subject before (baseline) and 2 h after drug administration (n = 17). Cannabis extract did not significantly alter heat pain thresholds, but there was a tendency toward a lower pain tolerance threshold.

Capsaicin Model

The intradermal injection of capsaicin induced a nearly maximum pain sensation in both groups with a peak value immediately after injection, followed by a consecutive decrease within 15 min to a moderate spontaneous pain level averaging VAS 1.3 (fig. 5). There was no difference in pain intensity between the two groups, but interestingly, pain showed a tendency to decrease more rapidly after cannabis compared with placebo (data not shown). The difference between the two groups was not statistically significant ($P > 0.05$).

The site of the flare area (fig. 6A) was traced onto a transparent plastic sheet 10 min after capsaicin injection, followed by the determination of the area of secondary hyperalgesia by pinprick (fig. 6B). Again, no significant differences between cannabis and placebo were found in the two areas.

Discussion

The cannabis extract used in the current study predominantly contained THC and CBD (2:1) at defined concentrations, together with a mixture of various other cannabinoid compounds that constituted less than 5% of the total cannabinoid content. In the past, the major constituent THC has been extensively shown to produce analgesic, antihyperalgesic, and antiinflammatory effects in animal experiments.

In our study, however, orally administered cannabis extract did not produce any significant analgesic or antihyperalgesic effects in two well-established acute human pain models, *i.e.*, sunburn and intradermal capsaicin. Within the sunburn erythema, but also in the surrounding area of secondary hyperalgesia and in the healthy skin of the contralateral leg, the heat and electrical pain thresholds were unaltered or even reduced after cannabis extract. In the area of primary hyperalgesia within the sunburn erythema, EPPT and EPTT at 250 Hz were significantly lower, indicating the induction of an unexpected hyperalgesic state in the cannabis group.

Although in our experiments the respective pain

Table 4. Area of Secondary Hyperalgesia: EPPT and EPTT

Parameter	Baseline	Cannabis	Placebo
EPPT 5 Hz, mA	0.729 ± 0.50	0.629 ± 0.53	0.583 ± 0.48
EPTT 5 Hz, mA	1.711 ± 1.27	1.107 ± 0.87	1.499 ± 1.24
EPPT 250 Hz, mA	2.477 ± 1.19	0.987 ± 1.08	1.029 ± 0.89
EPTT 250 Hz, mA	2.754 ± 2.09	1.925 ± 1.34	2.333 ± 1.45

Data are presented as mean ± SD of the reached intensity, when the subject stopped the further increase of the electrical stimuli. Pain thresholds were lower after cannabis, but differences *vs.* baseline (n = 17) and placebo (diazepam) were not significant ($P > 0.05$).

EPPT = electrical pain perception threshold; EPTT = electrical pain tolerance threshold.

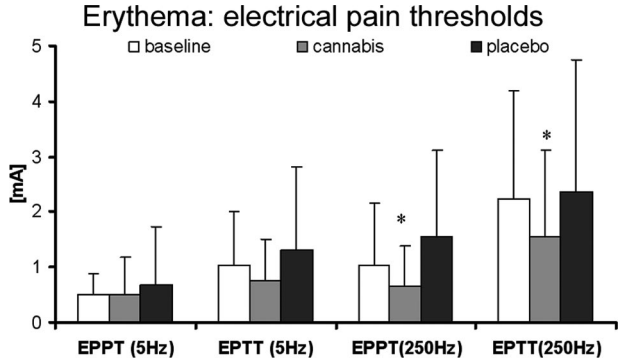

Fig. 4. Electrical pain thresholds within the sunburn erythema. Data are given as mean ± SD (n = 17) of the reached intensity 2 h after the study medication. Compared with placebo (diazepam), electrical pain perception threshold (EPPT) and electrical pain tolerance threshold (EPTT) were decreased for both frequencies, but significantly only for 250 Hz (* $P < 0.05$).

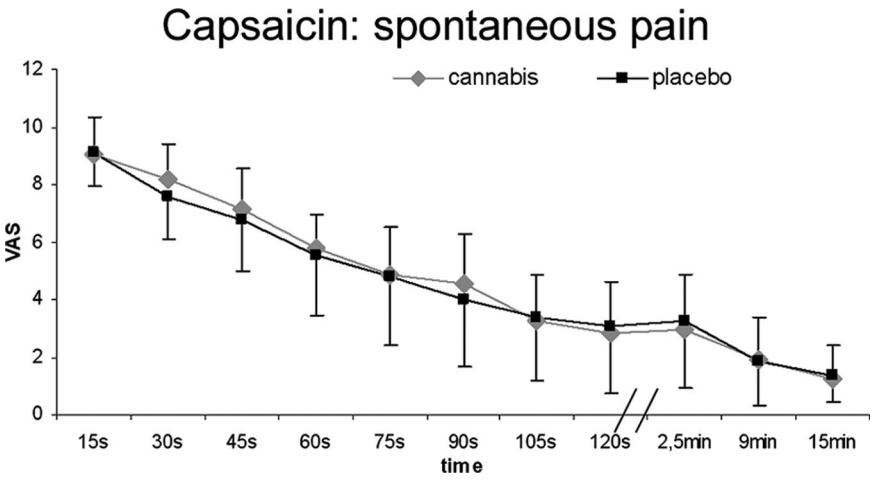

Fig. 5. Time course of spontaneous pain intensity (visual analog scale [VAS] of 0–10) after intradermal administration of capsaicin. Data are shown as mean values of pain intensity (VAS) after capsaicin injection. No significant effects of cannabis extract *versus* placebo (diazepam) could be observed.

thresholds were determined in pathologically sensitized skin, our results are remarkably consistent with the observations of a previous study by Naef *et al.*,[11] who found unaltered or decreased pain thresholds in normal skin of cannabis-experienced subjects after 20 mg oral THC. Using pressure, an ice-cold immersion test, and also heat and electrical stimulation in normal skin, their experiments substantially differed from our experimental setting but nevertheless produced similar results. Also, clinical trials with different oral cannabinoid preparations for postoperative acute pain management did not unequivocally support cannabinoid efficacy. In one study, nabilone (Cesamet®; Valeant Pharmaceuticals International, Aliso Viejo, CA), a synthetic THC analog, increased postoperative morphine consumption and pain, most likely reflecting a cannabinoid-induced hyperalgesic state.[28] Interestingly, increased pain was found in those patients receiving the highest dose of nabilone, indicating that higher doses may have a pronociceptive activity. In another study, no analgesic effect on postoperative pain after abdominal hysterectomy could be seen with a low oral dose of 5 mg THC. Because in that study no cannabinoid-specific side effects were observed and no plasma levels were determined, an insufficient gastrointestinal absorption of THC could not be ruled out.[9] Finally, although Holdcroft *et al.*[10] described some dose-dependent analgesic effects in postoperative pain using the same THC-standardized cannabis extract as in our study, only moderate analgesia could be achieved by oral administration of 10 mg THC plus 5 mg CBD. The higher doses of 15 mg THC plus 7.5 mg CBD were more effective but produced severe side effects and were therefore considered inappropriate. From these previous clinical data, the lack of an analgesic action in our experiments with 20 mg THC plus 10 mg CBD cannot be considered the result of inadequate analgesic dosage or insufficient gastrointestinal absorption. Moreover, the high levels of THC and its metabolites detected in the plasma of our probands and the occurrence of psychotropic side effects, although moderate and completely reversible by the end of the 8-h observation period, also argue for a sufficient bioavailability.

In our study, however, besides frequently observed side effects, such as sedation, nausea, and vertigo, only one subject of the 18 cannabis-naive volunteers (6%) experienced a transient psychotic episode. This low rate of psychotic symptoms was most likely due to the thoroughly performed psychiatric prescreening. Other authors reported severe psychotic episodes after 20 mg oral THC in up to 25% of cannabis-experienced subjects, but—in contrast to our study—no previous psychiatric screening was performed to exclude individuals at risk.[29] Although the occurrence of acute transient psychosis can never be completely ruled out, the different incidences in the former and in our study strongly suggest a mandatory psychiatric preevaluation for future trials with single high-dose administration of THC or cannabis extract.

In contrast to oral cannabinoids, smoked whole plant cannabis exerted analgesic effects not only in clinical

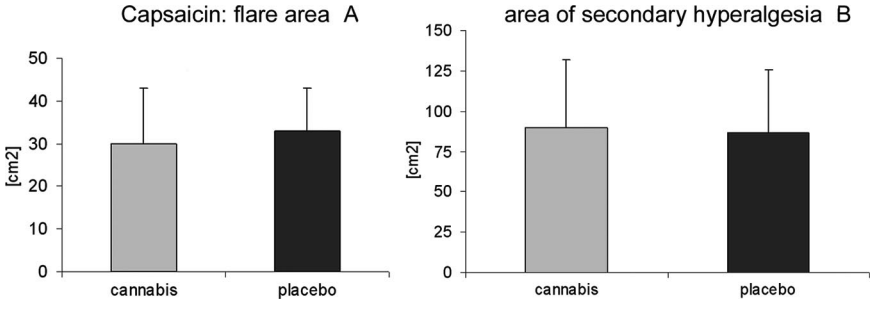

Fig. 6. Area of neurogenic inflammation (flare area) (*A*) and area of pinprick hyperalgesia (*B*). No significant difference between cannabis and placebo (diazepam) 15 min after intradermal capsaicin injection ($P < 0.05$). Data are given as mean ± SD (n = 17).

studies on chronic pain,[14] but also on acute pain.[13,14,30] One possible explanation for this apparent discrepancy could be the well-known pharmacokinetic differences of smoked *versus* oral cannabis, because inhaled cannabinoids do not undergo initial first-pass metabolism in the liver and quickly reach high concentrations at their target sites in the nervous system. In a recent study by Wallace *et al.*,[13] an analgesic effect of smoked cannabis on capsaicin-evoked spontaneous pain was reported, demonstrating a complex and not-well-understood dose dependence. In this study, analgesia was delayed, occurring 55 min but not 5 min after inhalation of a medium THC dose, but surprisingly, the highest THC dose caused hyperalgesia, which was somehow similar to our results. With respect to bioavailability, the hyperalgesia-producing high dose of smoked cannabis induced some threefold-higher and the analgesia-inducing medium dose induced twofold-higher mean plasma levels of THC compared with the mean peak levels reached after oral administration in our study. The lack of analgesic action in our experiments could be due to the lower THC peak levels and the slow increase in plasma and tissue concentration resulting from gastrointestinal absorption and first-pass effect, as clearly demonstrated by the individual as well as the mean plasma levels of THC, CBD, and the two major metabolites found in our study at the time of pain measurements. However, the mean levels of the first active metabolite, THC-11-OH, which is three times more potent than THC,[31,32] were three to four times lower after smoking compared with the concentrations measured in our trial. Hence, the high levels of THC-11-OH might have been responsible for the lack of analgesia and some hyperalgesic effects in our subjects by the same way as it has been suggested for the high THC levels measured in the inhalational study by Wallace *et al.*[13] However, in contrast to the report with smoked cannabis, we could not see any correlation between analgesic or hyperalgesic effects and THC, CBD, or metabolite levels at the time when pain measurements were performed. This argues against a simple pharmacokinetic explanation for the discrepant results of the two studies.

Comparing the two study designs, an effective blinding in a crossover study must be questioned, when cannabis or placebo cigarettes were smoked by cannabis-experienced individuals, who must have fulfilled the inclusion criterion of cannabis consumption within the past 6 months and were again intentionally exposed to high-dose cannabis just before the study experiments. Given the known fast psychotropic effects of cannabis smoking, any attempt at blinding experienced cannabis users in a crossover trial and exposing them to placebo *versus* low-, medium-, or high-dose THC-containing cigarettes seems impossible, in particular when testing was performed 5 or even 55 min after smoking. Therefore, a major impact on the results from Wallace *et al.*[13] by possibly biased expectations of the probands cannot be ruled out, because the analgesic effects seen in such studies might have been influenced by the unintended but inevitable unblinding of the subjects, in particular when every proband underwent high-dose cannabis exposure before the series of experiments.

With respect to the typical THC-mediated psychotropic actions caused by cannabis and cannabis extracts, 5 mg diazepam was used in our study as an "active placebo" to prevent the potential unblinding of the probands in a crossover design. Diazepam has no clinically relevant analgesic effect[33] but may give a cannabis-naive individual the impression of an active psychotropic drug. Therefore, the use of diazepam as an active placebo is unlikely to have negatively influenced the results of our study. As revealed by self assessment of our cannabis-naive probands, blinding was effective in our experimental setting.

The analgesic effects of smoked cannabis reported by Abrams *et al.* [14] for heat- and capsaicin-evoked dermal hyperalgesia cannot be compared directly with our experimental results, because all individuals tested in that study already had chronic human immunodeficiency virus–associated neuropathy. Therefore, although similar acute noxious stimuli have been used, the cannabis effects are not at all comparable with data obtained in healthy subjects of our study or the studies of Naef *et al.*[11] and Wallace *et al.*[13]

Only clinical trials in chronic pain patients have been published to date with the sublingual application of a THC/CBD-containing spray (Sativex®; GW Pharmaceuticals, Salisbury, United Kingdom), which produces pharmacokinetic and metabolic profiles more similar to those of smoking. As mentioned previously, these results from patients with multiple sclerosis,[18,34,35] chronic inflammatory pain,[36] and neuropathic pain[37] cannot be directly compared with our data obtained from an experimental human model of acute pain or with clinical acute pain conditions such as postoperative pain.

Based on our data and those from other studies on acute pain, the analgesic efficacy of oral THC-standardized cannabinoids seems to be considerably lower in humans than in animals. This discrepancy could be, at least partially, due to species differences, because endocannabinoid levels in rodents were reported to be four times lower than in humans, suggesting a lower sensitivity to endogenous and exogenous cannabinoid compounds in the latter. Moreover, because data from animal pain models are mostly based on observations of behavioral changes,[38,39] and because cannabinoid doses sufficient to produce relevant antinociception in rodents are similar to those inducing other behavioral effects, such as hypomotility and catatonia,[40,41] it may be difficult to clearly separate these effects from each other. Although there is no doubt that animal experiments are important and helpful tools for studying mechanisms of acute and

chronic pain, their predictive value for human conditions of pain and hyperalgesia remains limited.[42]

In conclusion, a surprising result of our study is the absence of any kind of analgesic activity of THC-standardized cannabis extract on experimentally induced pain and hyperalgesia using two different, well-established human models of acute pain caused by peripheral and central nociceptive mechanisms. In striking accordance with previous data from other experimental settings,[11,13,28] our results also seem to support the impression that high doses of cannabinoids may even cause hyperalgesia in certain acute pain conditions.

But even if cannabinoids might have some analgesic effects at certain dosage and under special circumstances,[10,13] their general use for acute pain management is limited by the apparent and not-well-understood existence of a small therapeutic window, and by the dose-dependent occurrence of mainly psychotropic side effects. With respect to the broad variety of available effective and evidence-based medicine–proven analgesics such as nonsteroidal antiinflammatory drugs or opioids, our results do not suggest the use of cannabinoids as appropriate analgesics for the treatment of acute nociceptive pain in humans. From our data, however, no final conclusion can be drawn about their potential therapeutic efficacy in certain chronic pain conditions. The respective mechanisms underlying the whole variety of chronic pain syndromes may considerably differ from acute nociception. The chronicity of pain has been shown not only to lead to multiple changes in peripheral and central neuronal processing,[43,44] but also to be associated with complex psychosocial phenomena, physical disorders, and functional disabilities. Recent clinical trials have indicated that oral and sublingual cannabinoids can be effective coanalgesics in chronic pain patients, improving not only pain intensity, but also coping behavior and quality of life.[18,34–37,45,46] Therefore, future clinical studies in chronic pain patients are required to define the actual role of cannabinoids in chronic pain management, whereas our results further argue against a relevant antinociceptive and/or antihyperalgesic effect of clinical doses of oral THC or standardized cannabis extract in acute nociceptive inflammatory pain or hyperalgesia.

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