

ORIGINAL ARTICLE

Delta-9-THC based monotherapy in fibromyalgia patients on experimentally induced pain, axon reflex flare, and pain relief

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ABSTRACT

Objective: Fibromyalgia (FM) is a chronic pain syndrome characterized by a distinct mechanical hyperalgesia and chronic pain. Recently, cannabinoids have been demonstrated as providing anti-nociceptive and anti-hyperalgesic effects in animal and human studies. Here, we explored in nine FM patients the efficacy of orally administered delta-9-tetrahydrocannabinol (THC) on electrically induced pain, axon reflex flare, and psychometric variables.

Research design and methods: Patients received a daily dose of 2.5–15 mg of delta-9-THC, with a weekly increase of 2.5 mg, as long as no side effects were reported. Psychometric variables were assessed each week by means of the West Haven-Yale Multidimensional Pain Inventory (MPI), Pittsburgh Sleep Quality Index (PSQI), Medical outcome survey-short form (MOS SF-36), the Pain Disability Index (PDI), and the Fibromyalgia Impact Questionnaire (FIQ). In addition, patients recorded daily, in a diary, their overall pain intensity on a numeric scale. Each week, pain and axon reflex flare was evoked

experimentally by administration of high intensity constant current pulses (1 Hz, pulse width 0.2 ms, current increase stepwise from 2.5–12.5 mA every 3 minutes) delivered via small surface electrodes, attached to the volar forearm skin.

Main outcome measures: Daily pain recordings by the patient, experimentally induced pain, and axon reflex flare recorded by a laser Doppler scanner.

Results: Five of nine FM patients withdrew during the study due to adverse side effects. Delta-9-THC had no effect on the axon reflex flare, whereas electrically induced pain was significantly attenuated after doses of 10–15 mg delta-9-THC ($p < 0.05$). Daily-recorded pain of the FM patients was significantly reduced ($p < 0.01$).

Conclusions: This pilot study demonstrated that a generalized statement that delta-9-THC is an analgetic drug cannot be made. However, a sub-population of FM patients reported significant benefit from the delta-9-THC monotherapy. The unaffected electrically induced axon reflex flare, but decreased pain perception, suggests a central mode of action of the cannabinoid.

Introduction

Fibromyalgia (FM) is a chronic pain syndrome of unknown origin. FM patients often report painful mechanical hyperalgesia and chronic pain at particular characteristic tender points¹. Medical treatment of FM includes therapy with, for example, opioids (i.e. oxycodon) or non-opioidergic analgesics (i.e. metamizol), psychotherapy with anti-depressive drugs, and physiotherapy². However, in some FM patients these treatments do not provide a relief of the clinical symptoms and alternative approaches are needed.

In animal studies, intrathecal administration of cannabinoids has demonstrated antinociceptive responses³. A proportion of peripheral analgesic effects were attributed to neuronal mechanisms acting through cannabinoid receptors, expressed on primary afferent neurons⁴, and peripheral administration of a cannabinoid receptor agonist revealed antinociceptive and antihyperalgesic effects in humans⁵. In addition, systemic medication with delta-9-tetrahydrocannabinol (THC) revealed some therapeutic effect in the treatment of cancer pain⁶, intractable pruritus⁷, nausea⁸, and anorexia⁹, including a mood enhancing quality during chemotherapy¹⁰, whereas oral medication with delta-9-THC failed to significantly reduce experimentally induced thermal pain¹¹. In an initial pilot study, with a small number of FM patients, we explored the potential effect of long-term medication with delta-9-THC (Dronabinol) on electrically induced pain, axon reflex flare responses, and daily estimated pain intensity.

Repetitive constant current stimulation with high intensity and low frequency induces in human skin the activation of nociceptive afferent units¹², particularly of mechano-insensitive 'silent' nociceptors¹³. Continuous excitation of such unmyelinated high-threshold and mechanically insensitive units elicits the development of an axon reflex flare¹² and pain¹⁴. Moreover, activation of these mechano-insensitive nociceptors gives rise to central sensitization in terms of secondary punctate hyperalgesia and allodynia development¹⁵. Experimentally induced development of secondary hyperalgesia and allodynia has been used as a neuropathic pain model. In the present study we adapted this experimental model to explore the development of the axon reflex flare and pain in FM patients prior to and during cannabinoid therapy with delta-9-THC. Apart from the psychophysical assessment of pain, electrically induced axon reflex flare was used as an objective parameter for peripheral nociceptor activation. The experimental protocol

was designed to reliably evoke central and peripheral effects, i.e. pain and axon reflex flare, in order to separately investigate the analgesic effects of delta-9-THC on both experimentally induced conditions and subjective daily-perceived pain ratings in FM patients.

Patients and methods

Ethical clearance

The study was approved by the human investigation committee of the Clinical Faculty Mannheim, University of Heidelberg, according to the declaration of Helsinki. Long-term cannabinoid medication with delta-9-THC was approved by the Federal Opium Department in Bonn (Germany) according to the national guidelines on narcotic law. Administration of a maximum dose of 20 mg delta-9-THC was permitted, and the treatment of FM patients with the drug approved. The inclusion of a placebo control group, however, was prohibited to avoid FM patients being untreated during study therapy. Moreover, the federal institution (Germany) prohibited the inclusion of healthy volunteers serving as a control group due to the putative side effects of the drug and consequent considerable impairments during a 3-month medication period.

Participants

Nineteen patients signed in at the Clinical Faculty Mannheim, Department of Anaesthesiology, for acute treatment of FM symptoms. Patients were informed in detail about the purpose of the study, the procedure, and the experimental protocol. A written informed consent form was obtained from all patients prior to the study.

Eight out of 19 patients were excluded from the protocol due to coronary heart disease, known side effects to cannabis, indispensable medication with opioids, or a contradiction for psychoactive drugs due to their psychosocial behavior. Eleven patients were diagnosed with widespread pain, in combination with tenderness of 11 or more out of 18 specific tender point sites, and thus fulfilled the criteria of FM according to the American College of Rheumatology¹. During the study, two FM patients were excluded from the trial at their own request, and five more patients were excluded due to intolerable side effects to delta-9-THC (i.e., sedation or daze). Thus, four FM patients (one male and three female, mean age 43 ± 12 years) tolerated delta-9-THC medication and completed the study.

Experimental procedure

Medication with delta-9-THC

All pain medication was stopped 3 weeks prior to the investigation. In the study, FM patients received a daily oral dose of 2.5–15 mg delta-9-THC. The dosage was increased weekly by 2.5 mg delta-9-THC, as long as no severe side effects (i.e. sedation) were reported. Patients' compliance was monitored by analysis of glucuronidated 11-nor- Δ^9 -tetrahydrocannabinol-9-carboxylic acid in authentic urine samples, using liquid chromatography–tandem mass spectrometry as described previously¹⁶.

Electrical stimulation protocol

Once a week, 24 hours after the last delta-9-THC medication and a day before any dose increase, two small surface electrodes (3 × 10 mm) were attached at a distance of 3 mm to the central volar forearm of the patient. Electrodes were connected to a constant current stimulator (Digitimer DS7A, Welwyn Garden City, UK) and a pulse generator (Rimkus Pulsgenerator PGI, Parsdorf, Germany). Threshold perception to electrical stimulation was determined and subsequent current pulses increased stepwise (1 Hz, pulse width 0.2 ms) every 3 min from 2.5 mA to 12.5 mA. The administration of constant current pulses induced an axon reflex flare and a sensation of stabbing pain at the stimulation site.

Assessment of experimentally induced pain and hypersensitivity

Pain sensation was rated on a numeric visual analogue scale (VAS) with the endpoints 0 (no sensation) and 10 (maximum pain imaginable) before and after each current increase. In accordance to earlier experiments, performed in healthy volunteers at higher current intensity (up to 90 mA) and of longer duration (120 minutes)^{14,17}, an adaptation of pain perception to the experimental paradigm was not observed.

Hypersensitive responses to touch (allodynia) and pinprick (hyperalgesia) were assessed as reported previously⁵. Briefly, touch allodynia was investigated by stroking the skin with a cotton pad at the stimulation site, and perceived sensation to the tactile stimulus was compared to that evoked similarly at the ipsilateral forearm. Any change of sensation was recorded as a yes/no answer. Pinprick hyperalgesia was investigated by means of a calibrated von Frey filament (160 mN, 0.25 mm in diameter) delivered five times perpendicular to untreated skin and in the vicinity of the stimulation site for comparison. The development of pinprick hyperalgesia was determined

by an instant change of sensation, described by the FM patient as increase in intensity and/or instant burning, pain or sourness induced by the pinprick. If hyperalgesia had developed, the spatial extension was assessed transversally and longitudinally in steps of 10 mm around the stimulation site. The borders were marked on the skin with a felt-tip pen and length of the longitudinal and transversal axes were documented for statistical analysis.

The patients' eyes were closed throughout the experiments exploring touch allodynia and pinprick hyperalgesia.

Measurement of vasodilatation

Axon reflex flare was recorded by a laser Doppler scanner (Moor Instruments, Axminster, UK) in 3-minute intervals and at a distance of 30 cm from the skin surface. One single scan required approximately 2.5 minutes, covering an area of 5 × 5 cm. Skin blood flow was assessed prior to the stimulation (baseline) and immediately after each current increase. Blood flow analysis was performed using the software package supplied by the manufacturer of the scanner (Moor Instruments, moorLDI version 3.08). Threshold value of skin perfusion was defined as mean blood flow + 3-fold standard deviation of all pixels which had been recorded in an area within 4 cm² of the baseline image. Perfusion values above the threshold were considered a significant increase of blood flow; pixels below the threshold were disregarded. The size of the axon reflex flare was calculated in each perfusion image by means of the number and area of pixels above the threshold.

Recording of psychometric variables in a patient diary

As reliable outcome measures used previously in psychophysical pain research^{18–20}, psychometric variables were assessed prior to study onset and after its finalization using the West Haven-Yale Multidimensional Pain Inventory (MPI) and the Pittsburgh Sleep Quality Index (PSQI); quality of life was assessed by means of a test battery based on the Medical outcome survey-short form (MOS SF-36), the Pain Disability Index (PDI), and the Fibromyalgia Impact Questionnaire (FIQ). Pain intensity was daily recorded by means of a numeric pain scale with the endpoints 0 (no pain) and 10 (maximum pain imaginable).

Statistics

For statistical analysis, electrically induced flare size and pain sensation, as well as psychometric variables of the patients' diaries, were analyzed as independent variables

by factorial ANOVA, using appropriate software (Statistica6.0, Statsoft Inc., Tulsa, US). Significance levels were $p < 0.05$. Significant differences of experimental flare and pain development were determined by Bonferroni *post hoc* tests. If not otherwise stated, all data are depicted as mean \pm SEM throughout.

Results

Seven out of the diagnosed and recruited 11 FM patients were excluded from the study. Two panelists were excluded at their own request prior to the first experiment. Five panelists had to be excluded due to severe side effects reported during delta-9-THC medication, which were primarily sedation, daze, fatigue or continuous tiredness. For data validity, all recorded values of experimentally induced flare and pain were included and evaluated with reference to the dose of medication for each FM patient. The numbers of patients being analyzed and plotted are stated in each figure and for each delta-9-THC concentration.

As depicted for one specimen in Figure 1, transcutaneously delivered constant current pulses with increasing intensity reliably evoked a widespread flare reaction in the patients' forearms.

Assessed touch evoked allodynia and pinprick induced hyperalgesia was not significantly affected by delta-9-THC medication (data not shown).

Electrical stimulation provoked an axon reflex erythema, dependent on the administered current intensity. A current of at least 5 mA was required to induce an axon reflex erythema, which gradually increased with higher current intensities (Figure 2). Under baseline

conditions, i.e. patients without medication ($n = 9$), maximum flare size was evaluated at $0.7 \pm 0.15 \text{ cm}^2$ (5 mA), $2.6 \pm 0.6 \text{ cm}^2$ (7.5 mA), $4.7 \pm 0.8 \text{ cm}^2$ (10 mA), and $6.0 \pm 0.7 \text{ cm}^2$ (12.5 mA). Administration of delta-9-THC did not attenuate the development of the flare reaction ($p = 0.9$, ANOVA). Even the highest concentrations of delta-9-THC (15 mg/d) administered for 3 months ($n = 4$) were effective in reducing the electrically induced flare reaction significantly (Figure 2). The detection limit for electrical stimulation was $1.0 \pm 0.1 \text{ mA}$ ($n = 9$) and did not alter significantly during delta-9-THC medication ($p = 0.1$, ANOVA, data not shown).

In response to the electrical stimulation, all patients reported a stabbing pain sensation that increased with higher current intensity. Without medication, current pulses of 5 mA exceeded pain thresholds and were estimated on the numeric scale at 3.4 ± 0.7 ($n = 9$). Medication with increasing doses of delta-9-THC attenuated experimentally induced pain significantly ($p < 0.05$, ANOVA, Figure 3). When compared to the baseline and 5 mg/d delta-9-THC medication, respectively, administration of 10 mg/d and 15 mg/d delta-9-THC significantly reduced pain ($p < 0.001$, Bonferroni *post hoc* test). In addition, continuous and long-term medication with 15 mg/d delta-9-THC attenuated pain perception significantly in comparison to baseline condition and low dose 5 mg/d delta-9-THC medication ($p < 0.05$, Bonferroni *post hoc* test).

All patients who completed the delta-9-THC therapy over 3 months ($n = 4$) experienced pain relief of more than 50%; mean numeric pain score was recorded at 2.8 ± 5 (Table 1). In comparison to baseline condition, and prior to the study, delta-9-THC treatment resulted

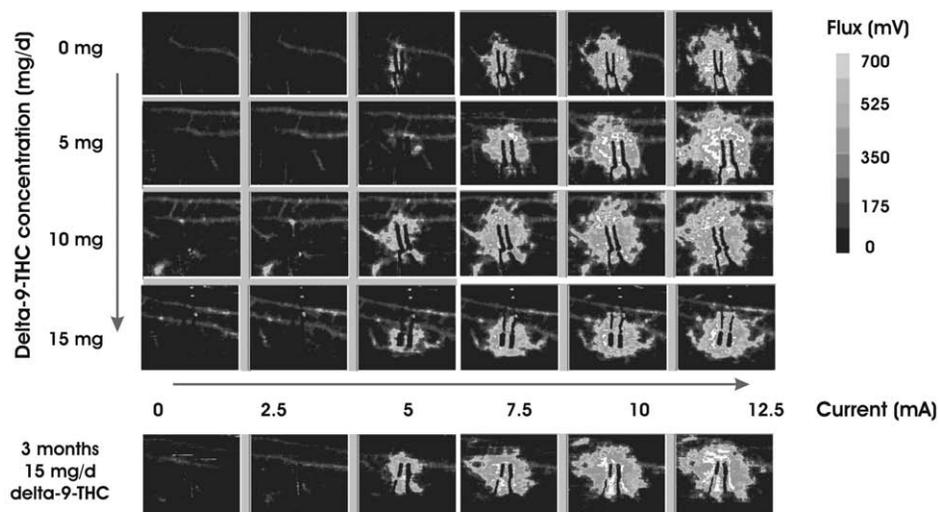


Figure 1. Sequence of laser Doppler blood flow images recorded in a specimen in dependence of applied current pulses (0–12.5 mA, 1 Hz, 0.2 ms pulse width, delivered in 3 minute intervals depicted from left to right) and the dose of delta-9-THC medication (concentration in mg/day, depicted from top to bottom). Even continuous intake of 15 mg delta-9-THC over 3 months had no effect on electrically induced flare responses (bottom line)

in significantly decreased pain with a mean reduction of 67% and an absolute median change of -5.3 from baseline to week 12 ($p < 0.01$, ANOVA). Values of PDI, FIQ, and MOS SF-36 did not change significantly in response to delta-9-THC medication.

Discussion

In the present study we investigated the effect of orally administered delta-9-THC on experimentally induced pain, axon reflex flare, and assessed daily psychometrical

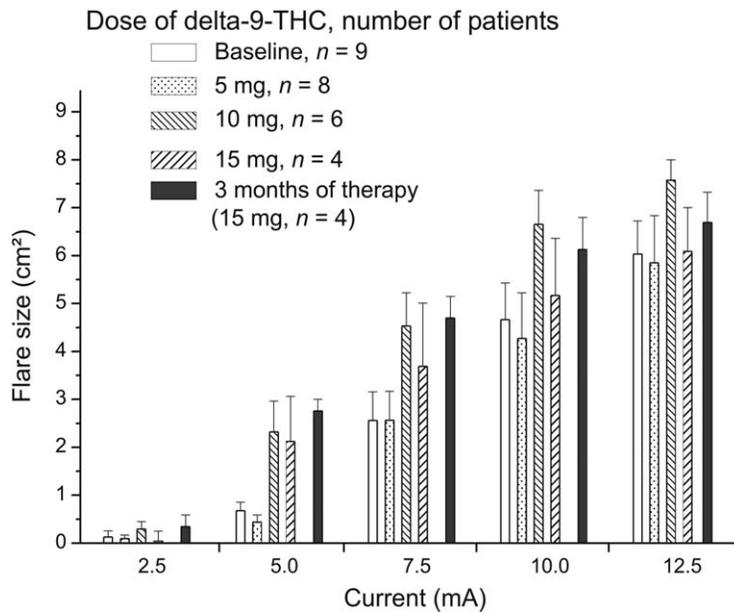


Figure 2. Electrically induced flare responses in FM patients (mean \pm SEM) receiving delta-9-THC monotherapy. Elevation of current intensity from 2.5–12.5 mA (1 Hz, pulse width 0.2 ms) induced a dose-dependent increase of the flare size. Delta-9-THC treatment had no significant impact on flare development. Note that increasing doses of delta-9-THC caused a decrease of participating FM patients due to unwanted side-effects

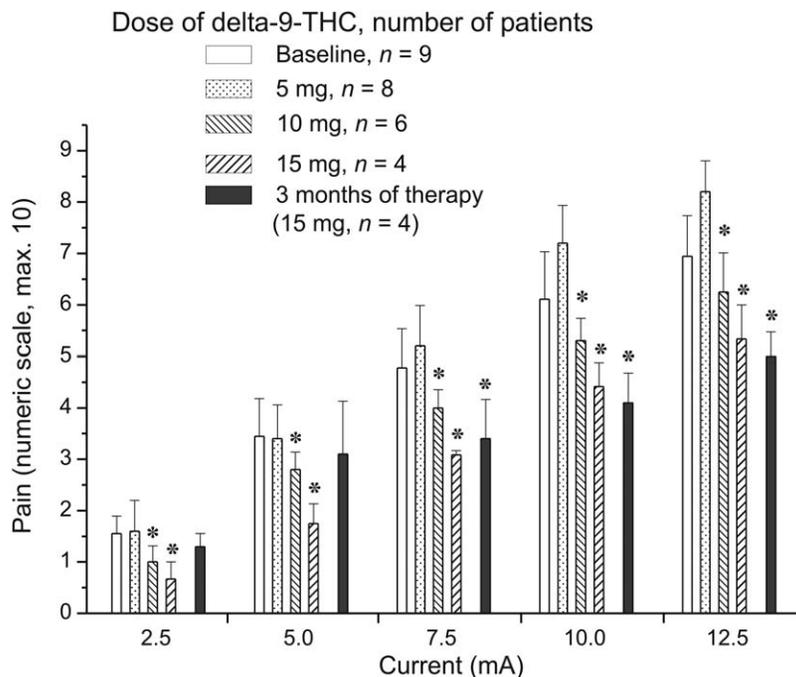


Figure 3. Magnitude pain sensation (mean \pm SEM) estimated by FM patients on a numeric scale (minimum 0, maximum 10) in response to electrical stimulation (2.5–12.5 mA, 1 Hz, pulse width 0.2 ms) and dependent on administered delta-9-THC concentration. Compared to baseline (no medication) or 5 mg delta-9-THC medication, administration of 10 mg and 15 mg delta-9-THC significantly reduced pain (* $p < 0.001$, Bonferroni post hoc test). Note that increasing doses of delta-9-THC caused a decrease of participating FM patients due to unwanted side-effects

Table 1. Summary of all psychometrically assessed variable scores (mean \pm SD) of the four FM patients that completed the study. Panelists received 15 mg delta-9-THC per day over 3 months, which significantly reduced pain perception by about 67% ($p < 0.01$, ANOVA)

	THC treatment		Difference	<i>p</i> -value
	Baseline	Long-term		
VAS	8.1 \pm 7.0	2.8 \pm 5.0	-5.3 \pm 2.3	< 0.01
PDI	34 \pm 10.0	23 \pm 11.0	-11 \pm 8.6	NS
FIQ	52 \pm 20.0	35 \pm 15.0	-17 \pm 8.8	NS
MOS SF-36				
General healthy	30 \pm 5.0	45 \pm 6.0	15 \pm 11.2	< 0.01
Social function	25 \pm 3.0	50 \pm 5.0	25 \pm 12.6	NS
Activity	7.5 \pm 5.0	7.1 \pm 4.0	-0.3 \pm 0.5	NS
Tiredness	2.5 \pm 1.2	2.9 \pm 1.3	0.25 \pm 0.4	NS
Sleep duration	2.1 \pm 1.8	1.5 \pm 0.7	-0.6 \pm 0.5	
Dizziness	-	-		
Vomiting	-	-		

THC = tetrahydrocannabinol; VAS = visual analogue scale; PDI = pain disability index; FIQ = fibromyalgia impact questionnaire; MOS SF-36 = medical outcome survey-short form; NS = not significant

variables in FM patients. Patients used a series of inventory questionnaires to record daily-assessed psychological variables. Once per week transcutaneous electrical nerve stimulation was conducted on the patients' forearms to evoke pain and axon reflex flare.

The development of the axon reflex flare was not affected by the delta-9-THC medication. In contrast, earlier studies reported that peripheral administration of cannabinoid agonists reduced histamine induced axon reflex flare²¹, capsaicin-induced pain⁵ and hyperalgesia induced by heat injury²². These apparent discrepancies are best explained by the experimental models being used. In contrast to the chemically evoked responses, the present study used a model of electrical stimulation to excite the axons of nociceptors. Axonal excitation is not affected by cannabinoids²³, thus a reduction of axon reflex flare should only be achieved by inhibition of neuropeptide release. There is conclusive evidence that the axon reflex flare development in humans is of peripheral neurogenic origin and based on the depolarization-induced neuropeptide release^{24,25}. In a previous study, cannabinoid 1 receptor agonists failed to inhibit KCl-induced neuropeptide release in rat dorsal root ganglia²⁶. In the present investigation, no particular peripheral effect of the delta-9-THC could be found through measures of the axon reflex flare. This finding is likely attributed to a lack of effect on neuropeptide release from peripheral nociceptive afferents by the oral administration of delta-9-THC.

A central or systemic mode of action of the drug is conceivable. This assumption is confirmed by the significant alleviation of both experimentally evoked and daily-perceived pain of the patients. In the present study, no concomitant analgesic treatment of the FM patients was allowed, and there was therefore no synergistic interaction of exogenous opioids with the

cannabinoid, as reported previously²⁷. However, the employed electrical pain model provokes the release of endogenous opioids that can be successfully antagonized by naloxone²⁸. A combined central effect of the orally administered cannabinoid and the release of endogenous opioids is therefore possible, as demonstrated recently *in vitro*²⁹. Even though a significant reduction of daily reported pain perception was reported by FM patients, no analgesic effects of cannabinoids were observed for acute pain thresholds⁵ or post-operative pain³⁰. The considerable high drop out rate of the FM patients due to unwanted side effects suggests that the findings of lowered pain experience might be the result of a bias effect of the patient receiving a putatively effective drug. Indeed, a placebo-controlled study design, which was, however, prohibited by the legislative assembly, would have obliterated such concerns. Thus, the present results cannot demonstrate a generally beneficial therapeutic efficacy of delta-9-THC medication in the treatment of FM patients. However, this pilot study revealed in a small number of FM patients the potential effect of delta-9-THC to alleviate chronic and experimentally induced pain.

The observation that about a third of the recruited FM patients profited from the delta-9-THC therapy, a central anti-nociceptive effect of cannabinoids³¹, may be important in at least a sub-population of FM patients. FM is a myofascial pain syndrome characterized by particular tender muscle points and mechanical hyperalgesia¹. No particular chemical or anatomical pathology has so far been clarified in those tender points, and it is believed that central sensitization processes contribute to the symptoms of FM^{32,33}. In healthy volunteers, hyperalgesia and central sensitization can be evoked by high current electrical stimulation of the skin¹⁷ and therefore have been used as a model to study neuropathic pain^{17,34}.

In the present study, cannabinoid therapy did not affect touch allodynia and pinprick hyperalgesia in FM patients, which may suggest that the beneficial effect of delta-9-THC on pain perception is independent from a neuropathic pain component in FM patients. On the other hand, cannabinoid-induced responses in FM patients have been related to a clinical endocannabinoid deficiency concept (CECD)³⁵. This concept is based on the observation that certain pathological conditions are attributable to a deficiency of neurotransmitters, for example Alzheimer's disease is attributable to a loss of acetylcholine activity. Accordingly, complementary administration of delta-9-THC in CECD patients would replace missing endocannabinoids to alleviate pain, dysphoria, and sleep disturbances beyond conventional pharmacotherapy³⁵. Our findings support the concept of a CECD syndrome, since in a sub-population of FM patients an impressive pain reduction was obtained. However, given that FM is a controversial psychosocial neurological condition, our results do not allow any specific pathophysiological conclusion on FM to be drawn.

Conclusion

Using an experimental model that reliably induces pain and axon reflex flare in humans, information about the mode of action of an analgesic drug can be made. Oral administration of delta-9-THC did not show analgesic properties in the periphery, but revealed – probably centrally mediated – pain attenuation in a subpopulation of FM patients. Nonetheless, the conclusion that delta-9-THC is a novel analgesic drug must not be drawn; a large-scale placebo-controlled study is required to clarify this issue.

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