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Acute Effects of a Single, Oral dose of d9-tetrahydrocannabinol (THC) and Cannabidiol (CBD) Administration in Healthy Volunteers

R. Martín-Santos[1,2,3]*, J.A. Crippa[1, 4], A. Batalla[2], S. Bhattacharyya[1], Z. Atakan[1], S. Borgwardt[1,5], P.Allen[1], M.Seal[1,6], K.Langohr[3,7], M. Farré[3], AW.Zuardi[4] and P.K. McGuire[1]

[1]*Department of Psychosis Studies, Institute of Psychiatry, King's College London, UK;* [2]*Department of Psychiatry, Institut Clínic de Neurociències, Hospital Clínic, IDIBAPS, CIBERSAM, Barcelona and Department of Psychiatry and Clinical Psychobiology, University of Barcelona, Spain;* [3]*Human Pharmacology and Neurosciences, Hospital del Mar Research Institute - IMIM, Barcelona, Spain;* [4]*Department of Neuroscience and Behavior, Faculty of Medicine of Ribeirão Preto, University of São Paulo, Brazil and INCT Translational Medicine, Ribeirão Preto, Brazil;* [5]*Department of Psychiatry, UPK, University of Basel, Switzerland;* [6]*Melbourne Neuropsychiatry Centre, The University of Melbourne, Australia;* [7]*Department of Statistics and Operations Research, Polytechnic University of Catalonia, Barcelona, Spain*

Abstract: *Rationale:* Animal and humans studies suggest that the two main constituents of *cannabis sativa*, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) have quite different acute effects. However, to date the two compounds have largely been studied separately.

Objective: To evaluate and compare the acute pharmacological effects of both THC and CBD in the same human volunteers.

Methods: A randomised, double-blind, cross-over, placebo controlled trial was conducted in 16 healthy male subjects. Oral THC 10 mg or CBD 600 mg or placebo was administered in three consecutive sessions, at one-month interval. Physiological measures and symptom ratings were assessed before, and at 1, 2 and 3 hours post drug administration. The area under the curve (AUC) between baseline and 3 hours, and the maximum absolute change from baseline at 2 hours were analysed by one-way repeated measures analysis of variance, with drug condition (THC or CBD or placebo) as the factor.

Results: Relative to both placebo and CBD, administration of THC was associated with anxiety, dysphoria, positive psychotic symptoms, physical and mental sedation, subjective intoxication (AUC and effect at 2 hours: $p<0.01$), an increase in heart rate ($p<0.05$). There were no differences between CBD and placebo on any symptomatic, physiological variable.

Conclusions: In healthy volunteers, THC has marked acute behavioural and physiological effects, whereas CBD has proven to be safe and well tolerated.

Keywords: Cannabis, Δ-9-THC-tetrahydrocannabinol, cannabidiol, unique dose, pharmacological acute effects, humans, induced anxiety, induced psychosis, review.

INTRODUCTION

Cannabis sativa preparations (marijuana, hashish, and others) are the illicit drugs most widely used in young people [1]. The plant has around 400 different chemical constituents, but two of its major psychoactive compounds are delta-9-tetrahydrocannabinol (THC) [2] and cannabidiol (CBD) [3,4].

THC acts as a partial agonist at specific endogenous cannabinoid receptors, termed CB1 and CB2, both members of the G-protein coupled receptor class [5]. The CB1 receptors are mainly expressed in the central nervous system, with a high density in the anterior cingulate, prefrontal cortex, medial temporal lobe and other areas [6] and are thought to mediate the majority of the effects of THC in the central nervous system. However, depending on the brain region, and whether the local CB1 receptors are expressed on neurons that release GABA or glutamate, THC can have either inhibitory or excitatory effects [7].

The acute administration of THC is associated with relaxation and enjoyment, but can also lead to unpleasant effects such as anxiety, psychotic symptoms, depression, apathy, and impairment of memory [8]. It has also been associated with impairments in learning, motor coordination, slowed reaction time, impaired concentration during complex tasks, deficits in some executive functions, and impairments in some aspects of verbal processing, such as verbal fluency [9,10]. THC administration can also produce an increase in heart rate and orthostatic hypotension. However, the acute effects of THC and their time of onset are subject to wide inter-individual variation and due to differences in route of administration, rate of absorption, metabolism and the subject's expectation of its effects [11].

In contrast, CBD has a low affinity for CB1 receptors [12] and its molecular mechanism of action remains poorly understood. It may facilitate endocannabinoid signaling by inhibiting the cellular uptake and enzymatic hydrolysis of endocannabinoids [12]. It can also bind to CB1 and to serotonergic (5HT1A) receptors, inhibit adenosine uptake, and can activate vanilloid (TRPV1) receptors at micromolar concentrations [12-16]. CBD is pharmacologically active and can have anticonvulsant, sedative, anxiolytic [3,4,17,18] and antipsychotic effects [4, 19-25]. Unlike THC, CBD does not have acute effects on motor or cognitive performance [26, 27], nor does it have significant effects on pulse rate or blood pressure [28, 29]. Functional neuroimaging studies have confirmed the neurophysiological effects of THC and CBD are distinct and opposite [30-34]. Moreover, co-administration of CBD and THC may alter the pharmacological effect of the THC, in that CBD potentiates some of THC's desirable effects but attenuates some of its negative effects [29, 34-36]. However, it is difficult to establish which

*Address correspondence to this author at the Department of Psychiatry, Institut Clínic de Neurociències, Hospital Clínic, IDIBAPS, CIBERSAM, and Department of Psychiatry and Clinical Psychobiology, University of Barcelona, Villarroel, 170. 08036-Barcelona, Spain; Tel: 34 932275400; Fax: 34 932275538; E-mail: rmsantos@clinic.ub.es

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CBD/THC ratios cause antagonism or potentiation, since other factors could interfere in the effects of these cannabinoids, such as the time between administrations of the two cannabinoids [37, 38]. Recent data showed the absence of significant differences between similar dose of oral THC and Sativex™, a plant extract with a 1: 1 proportion of both compound, on respect to subjective and physiological effects or pharmacokinetic [39, 40].

A better knowledge of the acute pharmacology effects of the two main compounds of the *cannabis sativa* may have implications for future research and therapeutics. We conducted a systematic review to assess the evidence for symptomatic and physiological effects of a single oral dose of THC and CBD in healthy volunteers. We reviewed literature in MEDLINE-PubMed database reporting studies with a cross-over, double-blind, placebo-controlled and randomised design in the last decade (2000-2011) (Table **1**). We found nine studies which met our inclusion criteria in which seven studies compared THC to placebo [41-47], one with Modafinil [46], another with an active placebo (Diazepam) [48], and one in front morphine using an active placebo (Diazepam) [48]. Three of the studies had used cannabis extracts (with small proportion of CBD) [41, 44, 48] and one had compared CBD with placebo [49]. None of the studies had compared both compounds within the same sample.

Therefore we aimed to carry out a study with the objective of evaluating the acute effects of THC and CBD in the same group of healthy volunteers. Subjects were studied after a single dose of THC, CBD or placebo in three consecutive sessions separated by an interval of one month. Given the findings from previous studies [29, 50], our main hypothesis was that THC and CBD would have distinct effects on symptoms and physiological measures.

MATERIAL AND METHODS

Subjects

The study was conducted in accordance with the Declaration of Helsinki, approved by the local research committee (The Joint South London and Maudsley Trust and Institute of Psychiatry NHS Research Ethics Committee). All participants signed an informed consent form after full explanation of the study was given and were paid for their participation. Thirty right-handed, English-speaking healthy male volunteers, aged 18 to 42 years, were recruited through advertisement in local newspapers, posters and word-of-mouth referrals. Alcohol and illicit drug use was assessed in detail using a semi-structured questionnaire [51], and used to screen potential participants. Only individuals who had used cannabis less than 15 times in their lifetime and had not experienced any undesirable effects after use, such as anxiety and/or psychotic symptoms were included. They were also required not to have used cannabis in the previous month and abstain from using cannabis over the study duration. Exclusion criteria included those who had used any other psychotropic drug on a regular basis or drank more than 21 units of alcohol per week or had any psychiatric, neurological or severe medical illness history. Those with a family history of a psychotic illness were also excluded.

Sixteen right-handed male volunteers, with a mean (SD) age of 26.4 (5.3) years (range 20-42) were selected for the study. They had completed a mean (SD) of 16.46 (3.9) years of education. Nine subjects (56.3%) reported having used cannabis less than 5 times in their lifetime, while 7 (43.8%) reported having used cannabis on between 5-14 occasions. None had a history of substance abuse or dependence defined according to DSM-IV criteria, except for nicotine dependence. Seven subjects were current smokers, but only two subjects smoked more than 10 cigarettes/day. All subjects had Reading scores on the WRAT-R test [52] within the normal range (mean (SD) = 98.67 (7.078); range 79-108).

Participants remained under close clinical observation in the research centre for at least 3 hours after each administration, with this period extended if they had not yet completely recovered. All participants agreed not to drive or use any machinery until the following day. A taxi was provided to take them home after each session.

Drugs

THC and CBD (approximately 99.6% and 99.9% pure, respectively) were supplied by THC-Pharm (Frankfurt, Germany) and STI Pharmaceuticals Ltd, (Brentwood, UK), and prepared by the Pharmacy Department of the Maudsley Hospital as identically appearing opaque capsules. The three drug conditions in the study were as follows: 10 mg THC, 600 mg CBD and placebo (flour). The doses of THC and CBD were selected on the basis of previous research [37,54-56] to produce a neurocognitive effect without provoking severe toxic, psychiatric or physical symptoms, which might confound interpretation of physiological and neuro-psychological data, or lead to the subject being unable to co-operate with the assessment.

Study Design

A crossover, double-blind, repeated measures design was used to compare the effects of THC, CBD and placebo. Participants were tested on three occasions at one-month intervals. The order of drug administration was pseudo-randomised to control for order effects. During the initial screening process, potential participants were familiarized with the testing procedures and questionnaires.

On each study day, subjects arrived at the research centre 1 hour before starting, having slept at least 6 hours and having had a standardised light breakfast. At each session, and before starting each assessment, urine samples were collected for screening for opiates, cocaine, amphetamines, benzodiazepines and THC using immunometric assay kits. None of the participants tested positive on any of the sessions. An indwelling intravenous catheter was then inserted into a subcutaneous vein in the forearm of the non-dominant arm. Thereafter, subjects remained seated in a quiet room throughout the session. Each drug was administered approximately after one hour of basal assessment.

Symptomatic Effects

Symptoms were evaluated at baseline and at 1, 2 and 3 hours after drug administration, using the Positive and Negative Psychotic Syndrome Scale (PANSS) [57], assessed by an experienced psychiatrist, and using a set of self-administered scales (below). The PANNS [57] a 30-item rating instrument was used to assess psychotic symptoms, with ratings based on a semi-structured clinical interview. Scores for each item range from 0 (absent) to 7 (extreme), and yield sub-scores for positive, negative, and general psychopathology domains. The self-administered scales comprised a 16-item version of the Visual Analogue Mood Scale (VAMS) [58], with four subscales: mental sedation or intellectual impairment, physical sedation or bodily impairments, anxiety effects and other types of feelings or attitudes. We also used the Addiction Research Centre Inventory (ARCI 49 item short form), a standardised measure of drug effects developed by Martin *et al* (1971) [59], comprising 49 true/false statements describing the subjective effects of various classes of substances. It has five empirically derived scales, measuring drug-induced euphoria (morphine-benzedrine group: MBG), stimulant-like effects (amphetamine group: A), intellectual efficiency and energy (benzedrine group: BG) and sedation (phenobarbital-chlorpromazine, alcohol group: PCAG), and dysphoria and somatic effects (lysergic acid: LSD). The Spielberger State Anxiety Inventory (STAI-T/S) [60] was used to assess state anxiety at hourly intervals, with subjects completing 20 items on current feelings and 20 on feelings in general.

Physiological Measures

Non-invasive systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate were recorded at 1 hour before administration, immediately before drug administration (time 0, base-

Table 1. Systematic review (MEDLINE-PubMED, 2000-2011) of cross-over, double-blind, placebo-controlled, randomized studies of subjective and physiological effects of a single oral dose, THC, CBD, administration in healthy volunteers*.

Author (year)	Inclusion (In) /Exclusion (Ex)** criteria	M/F	M (SD) range	Drugs administered	Dose mg	Measures hours	Clinical tools	Symptomatic effects		Physiological effects	Plasma concentrations ng/mL (Mean (SD)
								Increased	Decreased		
Sugarman *et al.* (2011) [46]	In: Healthy occasional volunteers THC+urine Ex: Any abuse/depend. Current psychiatric disorder Physical illness	11/1	33.7 (7.7)	THC (dronabinol) +Placebo Modafinil +Placebo THC+Modafinil Placebo	15 +400 15+400	Basal, ½, 1, 1½, 2½, 3, 3½, 4, 4½ & 5h	ARCI DEQ POMS BP HR	*THC* ARCI (sedation, dysphoria) DEQ ("feel high", "feel sedated", & "feel the drug strength")	*THC* POMS (vigor, depression) *THC +Modafinil* ARCI (euphoria)	*THC* HR increase Systolic BP low *THC +Modafinil* HR>increase	NA
Roser *et al.* (2008, 2009; Nadulski *et al.*, 2005 a,b) [41, 67-69]	In: Healthy occasional volunteers Ex: Any abuse/depend. Current/past psychiatric disorder Positive urine analysis Pregnancy	12/12	27.9 (2.9) 18-45	THC Cannabis extract Placebo	10 THC:10 CBD:5.4	Basal, ½, 1, 1½, 2, 4, 7, 9 & 24h	AIR FTA NA	*THC* AIR (subjective level of intoxication) *Cannabis ext* AIR Both similar	-	-	*THC* peak at 2h slightly > in F Similarly results with *Cannabis ext.* (THC and CBD).
Menetrey *et al.* (2005) Favrat *et al.* (2005) [42,70]	In: Healthy occasional volunteers Ex: Any abuse/depend. Current/past psychiatric disorder Physical illness	8/0	22-30	THC (dronabinol) Milk decoction Placebo	20 THC:16.5 THC:45.7 THC:1% CBD:0.4%	Basal, 1, 1½, 4, 5½, 7, 10 & 24h	VAS BP HR Conjuntival reddening	*THC & decoction* VAS (strong feeling of high intoxication) > after the highest dose *Decoction of 45.7 mg* > Nausea and vomiting *Two subjects excluded for anxiety (decoction 16.5 mg) and psychotic symptoms (dronabinol)*	-	*THC & decoction* HR slight/ moderate increased & conjunctival reddening	The highest mean THC was after ingestion the highest milk decoction.
Crippa *et al.* (2004) [49]	In: Healthy occasional volunteers Ex: Any abuse/depend. Personal/family current/past psychiatric disorder Physical illness Positive urine analysis	10/0	29.8 (5.1) 25-42	CBD Placebo	400	-½ (basal), 0, 1, & 1¼ h	VAMS NA	*CBD* VAMS (mental sedation)	*CBD* VAMS (subjective anxiety)	-	NA

(Table 1) Contd....

Author (year)	Inclusion (In) /Exclusion (Ex)** criteria	M/F	M (SD) range	Drugs administered	Dose mg	Measures hours	Clinical tools	Symptomatic effects		Physiological effects	Plasma concentrations ng/mL (Mean (SD)
								Increased	Decreased		
McDonald *et al*. (2003) [43]	In: Healthy occasional volunteers Ex: Any abuse/depend. Current/past psychiatric disorder Physical illness Low level education BMI: out of 19–26 kg/m^2 Positive urine analysis Pregnancy	18/19	23 (4.5) 18-45	THC (dronabinol) Placebo	7 15	Basal, 1/3, 11/3 & 21/3h	DEQ ARCI POMS BP HR	*THC* ARCI (stimulant-effects, marijuana-like effects, dysphoria, euphoria, somatic effects & sedation) DEG dose-dependently ("feel drug," "feel high", & "want more") POMS dose-dependently (anxiety, fatigue, anger, & confusion)	*THC* ARCI (intellectual efficiency and energy)	*THC* HR increase dose dependently BP was not affected	NA
Wachtel *et al*. (2002) [44]	In: Healthy occasional volunteers Ex: Any abuse/depend. Current/past psychiatric disorder Physical illness Low level education BMI: out of 19–26 kg/m^2 Pregnancy	7/5	23 (4) 18-31	THC Whole-plant marijuana, Placebo	8.4 16.9 8.4 16.9	Basal, ½, 1, 1½, 2, 2½, 3, 4 & 5h	VAS DEQ POMS BP HR RR BT	*THC dose-dependent* DEQ, ARCI (marijuana subscale & sedation) > marijuana group *THC-High condition* ARCI (stimulant effect, dysphoria & euphoria) > marijuana group *Marijuana* DEQ & ARCI (marijuana scores and sedation) dose-dependently *Marijuana-High condition* VAS (sedated, drowsy and tired)	-	Any relevant physiological effect	*THC* increases dose dependent 1h after *11-OH-THC* after 1.5h *THC-High condition* > levels than marijuana-High condition
Curran *et al*. (2002) [45]	In: Healthy occasional volunteers Ex: Any abuse/depend Current psychiatric disorder Physical illness Any drug use Positive urine analysis	15/0	24.2 (2.1) 18-30	THC (dronabinol) Placebo	7.5 15	Basal, 1, 2, 4, 6, 8, 24 & 48h	VAMS VAS NA	*THC* VAMS (drowsiness, anxiety) VAS (dizziness, dry mouth, palpitation and stoned feeling) No residual effects were found at 24h and 48h	*THC* VAMS (memory, concentration)	*THC* HR increase on the high dose	*THC* peak at 2h after both high and low dose. *11-OH-THC* levels same pattern. Levels at 24 & 48h were below limit detection

(Table 1) Contd....

Author (year)	Inclusion (In) /Exclusion (Ex)** criteria	M/F	M (SD) range	Drugs administered	Dose mg	Measures hours	Clinical tools	Symptomatic effects		Physiological effects	Plasma concentrations ng/mL (Mean (SD)
								Increased	Decreased		
Kaufmann *et al.* *** (2010; Kraft *et al.* 2008) [48, 66]	In: Healthy cannabis and BDZ naïve volunteers Ex: Any abuse/depend. Current or past psychiatric disorder Physical/pain illness Any drug use Positive urine analysis Pregnancy	0/16	23.6 (2.7) 19-29	Cannabis extract Active placebo (diazepam)	THC:20 THC:CBD: 2:1 Other can.<5% 5	Basal, every hour up to 8h	VAS BPRS BP HR BT PO	*THC* VAS (tiredness, dizziness drowsiness, feeling high) max. after 2h *One subject excluded for severe acute psychotic symptoms*	*THC* BPRS (emotional withdrawal, motor retardation, poor affective response and disturbance of orientation) after 3h	*THC* HR increase from baseline & placebo	*THC & CBD* peak were found between 2h and 4h Low levels of THC and high levels of metabolites. Intersubject variability for both cannabinoids
Naef *et al.* *** (2003) [48]	In: Healthy naïve volunteers Ex: Any abuse/depend. Current/past psychiatric disorder Physical illness Positive urine analysis Pregnancy Hypersensitivity to cannabinoids/ opioids,	6/6	M:27 (11) F: 25 (7)	THC (dronabinol), Morphine THC + morphine,	20 30 20+30	Basal, every hour up to 8h	VAS for pain BP HR PO	*THC* VAS (transient sleepiness, confusion, alt. perception, anxiety & aggression) VAS (pain) *THC + morphine* VAS (hyperalgesia effect was reversed) compared to morphine session	*THC+morphine* (euphorigenic & hallucinogenic effects) compared to THC session Nausea and vomiting > morphine session	*THC* HR increase *THC+morph* BP (systolic & diastolic) PO decrease	*THC* peak at 1-2h *11-OH-THC* peak at 2h and *THC-COOH* at 2-4h Low levels of *THC* and high levels of metabolites *THC+ morphine* Levels of THC were > than THC alone. *THC* plasma levels correlated with side effects

* The MEDLINE-PubMed database (2000-2011) was searched to locate articles using the keywords cross-over, placebo-controlled, randomized studies, single oral dose, healthy, physiological effects, subjective effects, delta-9-tetrahydroccaninol, THC, cannabidiol, CBD, and Boolean operators. Initially we found 20 studies. We excluded five studies for methodological aspects: Not cross-over design (Bergamaschi *et al*., 2011), open design (Ploner *et al*., 2002), no randomized design (Leweke *et al*., 2000), healthy volunteers with cannabis use more than 15-20 times (Stokes *et al*., 2010, 2009). When the data from a single subject sample were reported in separate publications, these were treated as a single study with multiple independent variables (Kraft *et al*., 2008, Roser *et al*., 2009, Nadulski *et al*., 2005a,b).

** Smoking tobacco was allowed in almost all studies.

*** These studies included cannabis naïve subjects because the objective was to evaluate analgesic properties in experimental pain models.

M/F= Male /Female. Symptomatology rating scales: AIR = Analogue Intoxication Rating Scale; ARCI = Addiction Research Centre Inventory; DEQ = Drug Effects Questionnaire; POMS = Profile of Mood States; VAMS = Visual Analogue Mood Scale; VAS = Visual Analogue Scale; STAI = State-Trait Anxiety Inventory; ASI = Addiction Severity Index; BPRS = Brief Psychiatric Rating Scale. Physiological measures: BP = blood pressure; BT = body temperature; HR = heart rate; min. = minute; PO = pulse oxymetry; RR = respiration rate.

line) and at 1, 2 and 3 hours after administration of drug. Blood pressure was measured when the subject had been sitting for at least 15 minutes. Heart rate and blood preassure were monitorised through a digital recorder and an automated arm cuff.

THC Concentrations

Blood samples for determination of THC, 11-hydroxy-delta 9-THC (11-OH-THC), and 11-nor-delta-9-tetrahydrocannabinol (THC-COOH) whole blood concentration were collected during each experimental session at baseline, and at 1, 2 and 3 hours after drug administration. THC is converted by microsomal hydroxylation to 11-OH-THC, which is both a key intermediate for further metabolism to THC-COOH by liver alcohol-dehydrogenase enzymes and a potent psychoactive metabolite [61,62]. Whole blood THC, 11-OH-THC, and THC-COOH concentrations (ng/mL) were measured by immunoassay. Positives were confirmed by gas chromatography-mass spectrometry (GC/MS) or GC/MS/MS.

Data Analysis

Statistical analyses of these measures were carried out using SPPS (v.15) by two of the researchers (RMS and KL) blind to the drug conditions. The various measures obtained from the experimental sessions (symptomatic, physiological, and drug level data) were transformed to permit analysis of the differences in each variable relative to baseline. For each variable, the area under the curve (AUC) between baseline and 3 hours was calculated using the trapezoidal rule. The maximum absolute change from baseline at 2 hours was also determined. The AUC and the effect at 2 hours were analysed using a one-way repeated measures analysis of variance with drug condition (THC or CBD or placebo) as factor. When ANOVA showed significant effects for drug condition, post-hoc multiple comparisons were performed, using the Tukey's test for repeated measures. Correlations between whole blood levels of the drugs and its metabolites and statistical significant symptomatic effects, and physiological measures were analysed using Spearman's correlation coefficient. Differences associated with P-values lower than 0.05 were considered to be statistically significant. When necessary, Bonferroni multiple testing correction test was used.

RESULTS

Symptomatic Effects

Table **2** shows that there were highly significant differences between the effects of the THC in comparison to CBD and placebo. THC produced changes on positive and negative psychotic symptoms, and general psychopathology (PANSS), anxiety (STAI-S), dysphoria (ARCI), sedation (VAMS, ARCI), and the level of subjective intoxication (ASI, ARCI), as indexed by both the AUC and by the effect at 2 hours ($p<0.001$). There was also difference on the VAMS anxiety ratings, which was significant at 2 hours ($p<0.03$) between THC and CBD, but not in the AUC analysis. Some volunteers, 5 (33%) showed severe effects and became markedly paranoid and anxious, but there was a wide inter-subject variability, with a wide range of scores on the PANSS positive scale. Pair-wise comparisons revealed significant differences between the effects of THC relative to both placebo, and to CBD (Table **2**). In contrast, there were no significant differences between the effects of CBD and placebo on any variable. The transient psychotic symptoms observed had resolved spontaneously within two hours. No psychopathological symptoms were reported on follow-up at next day, 1 and 3 weeks later.

(Figs. **1**, **2**, **3** and **4**) show the effects of the drugs on each measure (ASI, STAI-S, VAMS, ARCI, and PANNS) at 1, 2, and 3 hours post administration.

PHYSIOLOGICAL EFFECTS AND PLASMATIC CONCENTRATIONS OF THC AND CBD

Physiological Parameters

There were significant differences between drug effects on heart rate (Table **3**; Fig. **5**). Pair-wise comparisons showed that this reflected an increase in heart rate with THC relative to both placebo, and to CBD (placebo vs. THC: $p=0.0491$; THC vs. CBD: $p=0.0133$; placebo vs. CBD: $p=0.8596$). There was also a trend ($p<0.07$) towards difference in the drug effects on diastolic blood pressure at 2 hours (Table **3**).

Blood Levels

Mean (SD) whole blood levels of THC at 1, 2 and 3 hours after administration were 0.5 (0.8) ng/mL and 0.67 (0.66) ng/mL, and 0.44 (0.40) ng/mL, respectively. Mean (SD) whole blood levels of CBD at the same time points were 0.36 (0.64) ng/mL, 1.62 (2.98) ng/mL and 3.4 (6.42) ng/mL, respectively. Levels of 11-OH-THC and THC-COOH were elevated after administration of THC (but not CBD or placebo) and followed a similar time course (Fig. **6**).

Relationship between Blood Levels and Acute Symptomatic Effects

Both the level of subjective intoxication (ASI) and the PANSS total score (PANSS-TS) were directly correlated with THC-COOH levels at 1 hour post drug administration ($rho=0.665$; $p=0.009$; $rho=0.687$; $p=0.007$), and with THC levels at 3 hours post drug administration ($rho=0.760$; $p=0.002$; $rho=0.731$; $p=0.003$). Negative symptom levels (PANSS-N) also showed a positive correlation with both THC and 11-OH-THC levels at 3 hours post drug administration ($rho=0.813$; $p<0.001$; $rho=0.727$; $p=0.003$). We did not find significant correlation between heart rate and neither THC, 11-OH-THC nor THC-COOH whole blood levels.

DISCUSSION

Acute Symptomatic Effects

The administration of a single oral dose of THC produced the typical transient effects previously described for this substance in an experimental laboratory setting: feelings of anxiety, euphoria, dysphoria and subjective intoxication. Positive and negative psychotic symptoms were also evident in some, but not all subjects, again consistent with previous studies [63-65]. In the review done, seven of nine studies described "feel high", dysphoria, and subjective intoxication [41,42-44,46,48,66-69] (Table **1**). The intensity of symptomatology appeared to be dose-dependent [42, 44]. Moreover, from the 146 subjects involved in the review, 3 (2.1%) were excluded because they presented severe acute psychotic symptomatology during the study [42, 58, 70]. In our study, 5 (33%) subjects presented transient psychotic symptomatology in the THC session, which resolved spontaneously in two hours. This variabilility probably reflects differences in individual, or genetic susceptibility to THC proness to psychosis [71, 72].

Although studies in both experimental animals [73-77] and healthy volunteers [18, 29, 34, 49,78,79] have shown that CBD has anxiolytic properties, there were remarkably few differences between the effects of CBD and placebo on anxiety [17], save for a reduction in the VAMS anxiety scale at 2 hours post administration. However, in such previous human studies, the anxiolytic effect of CBD has only been evident in subjects in whom anxiety had already been induced experimentally, in contrast to the subjects in the present study. In addition, in animal models, the effect of CBD on anxiety appears to follow an inverted U-shaped dose-response curve [4, 75]. The dose of CBD used in the present study was higher than in previous human anxiety experimental studies (60-300 mg/day), [18, 29, 34, 49,78] and so may have exceeded the dose associated with a clear anxiolytic effect. Unlike THC, CBD had no effects on sedation, intoxication, mood or psychotic symptoms. These data suggest that CBD alone has remarkably few symptomatic effects in non-anxious healthy subjects, which is important in relation to the potential therapeutic utility of CBD in neurology, psychiatry and other fields of medicine [4, 24]. Recently, a double-blind, randomised study showed that CBD reduces anxiety induced by a simulation public speaking test in a group of patients with generalized social anxiety disorder to a similar response as healthy controls [79].

Physiological Measures

THC increased the heart rate as observed in other studies [42, 43, 45-48], but did not produce an increased systolic and diastolic blood pressure or an orthostatic hypotension, although there was a tendency for an effect on diastolic blood pressure [11]. This may reflect an effect of the THC mediated by sympathetic activation and cholinergic inhibition [80]. As expected from previous investigations [28, 29], CBD did not have any significant physiological effects.

Table 2. Results of Symptomatic Effects Comparisons after a Single Oral dose of Placebo, THC, CBD and Placebo Administration with Respect to the Area Under the Curve (AUC) and Effect at 2 Hours

	AUC				Effect at 2 hours			
	F	**p**		**p***	**F**	**p**		**p***
Symptomatic effects								
ASI	7.81	0.002	1	<0.001	14.33	<0.001	1	<0.001
			2	0.929			2	0.778
			3	0.003			3	<0.001
STAI-S	6.20	0.006	1	0.002	10.50	0.001	1	<0.001
			2	0.455			2	0.354
			3	0.055			3	0.005
VAMS								
Anxiety	2.46	0.105			3.97	0.03	1	0.179
							2	0.634
							3	0.020
Mental sedation	4.67	0.018	1	0.010	6.89	0.004	1	0.001
			2	0.517			2	0.739
			3	0.166			3	0.015
Physical sedation	3.67	0.039	1	0.019	6.18	0.006	1	0.002
			2	0.374			2	0.417
			3	0.358			3	0.084
Other feelings	0.45	0.64			0.20	0.816		
ARCI								
Stimulant-like effects-A	2.42	0.111			2.86	0.076		
Euphoria-MBG	2.22	0.314			2.73	0.084		
Dysphoria-LSD	9.16	0.001	1	0.001	15.03	0.001	1	<0.001
			2	0.963			2	0.535
			3	<0.001			3	<0.001
Intellectual efficiency-BG	4.76	0.019	1	0.024	2.85	0.077		
			2	0.996				
			3	0.023				
Sedation-PCAG	8.33	0.002	1	<0.001	11.32	<0.001	1	<0.001
			2	0.928			2	0.845
			3	0.003			3	<0.001
PANNS								
General psychopathology	9.10	<0.001	1	<0.001	10.71	<0.001	1	<0.001
			2	0.668			2	0.91
			3	0.003			3	<0.001
Positive symptoms	9.14	0.001	1	<0.001	5.37	0.010	1	0.010
			2	0.966			2	0.975
			3	<0.001			3	0.019
Negative symptoms	5.65	0.008	1	0.002	5.73	<0.001	1	0.002
			2	0.359			2	0.317
			3	0.109			3	0.131

ASI= Subjective level of intoxication; STAI-S=Spielberger State Anxiety Inventory; VAMS= Visual Analogue Mood Scale; ARCI= Addiction Research Center Inventory; PANNS= Positive and Negative Psychotic Symptomatology Scale

*Pair wise comparisons: 1) placebo vs. THC, 2) placebo vs. CBD, and 3) THC vs. CBD

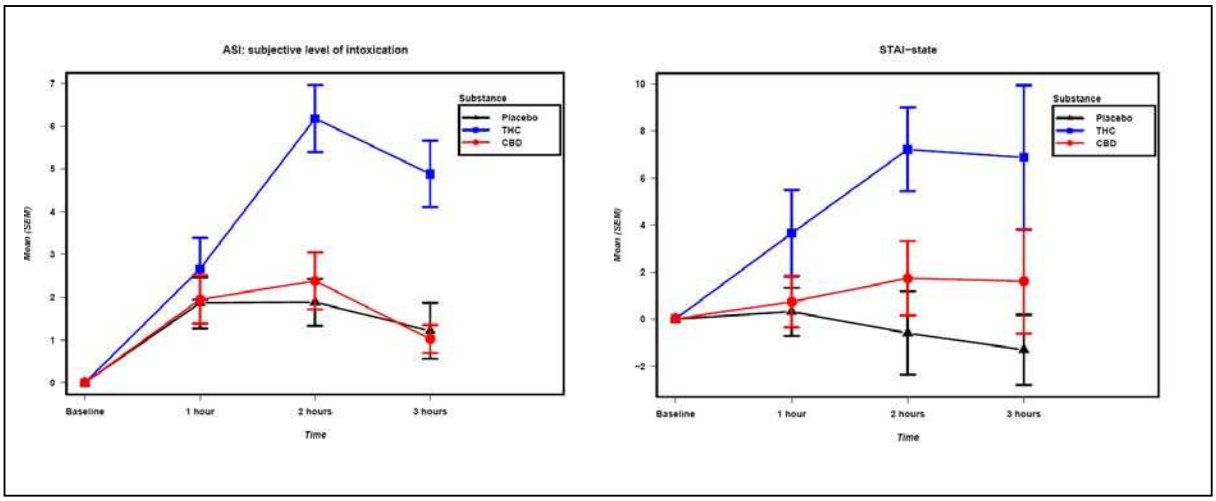

Fig. (1). Changes from baseline over time in the level of subjective intoxication (ASI) score and the level of anxiety (STAI-S) after oral administration of 10 mg THC, 600 mg CBD, and placebo. The figure shows mean (±SEM) values.

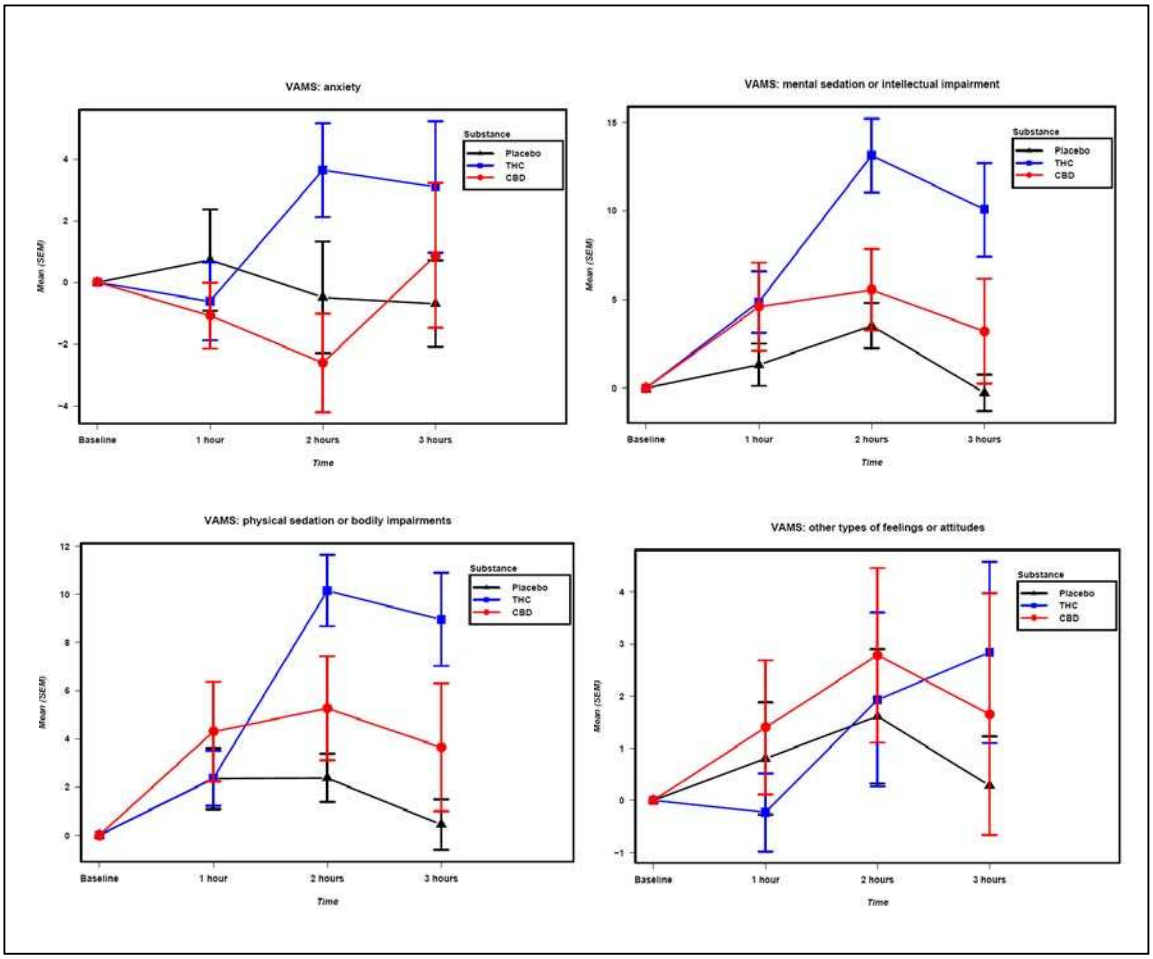

Fig. (2). Changes from baseline over time in anxiety level, mental and physical sedation and other feelings (VAMS) after administration of 10 mg THC, 600 mg CBD, and placebo. The figure shows mean (±SEM) values.

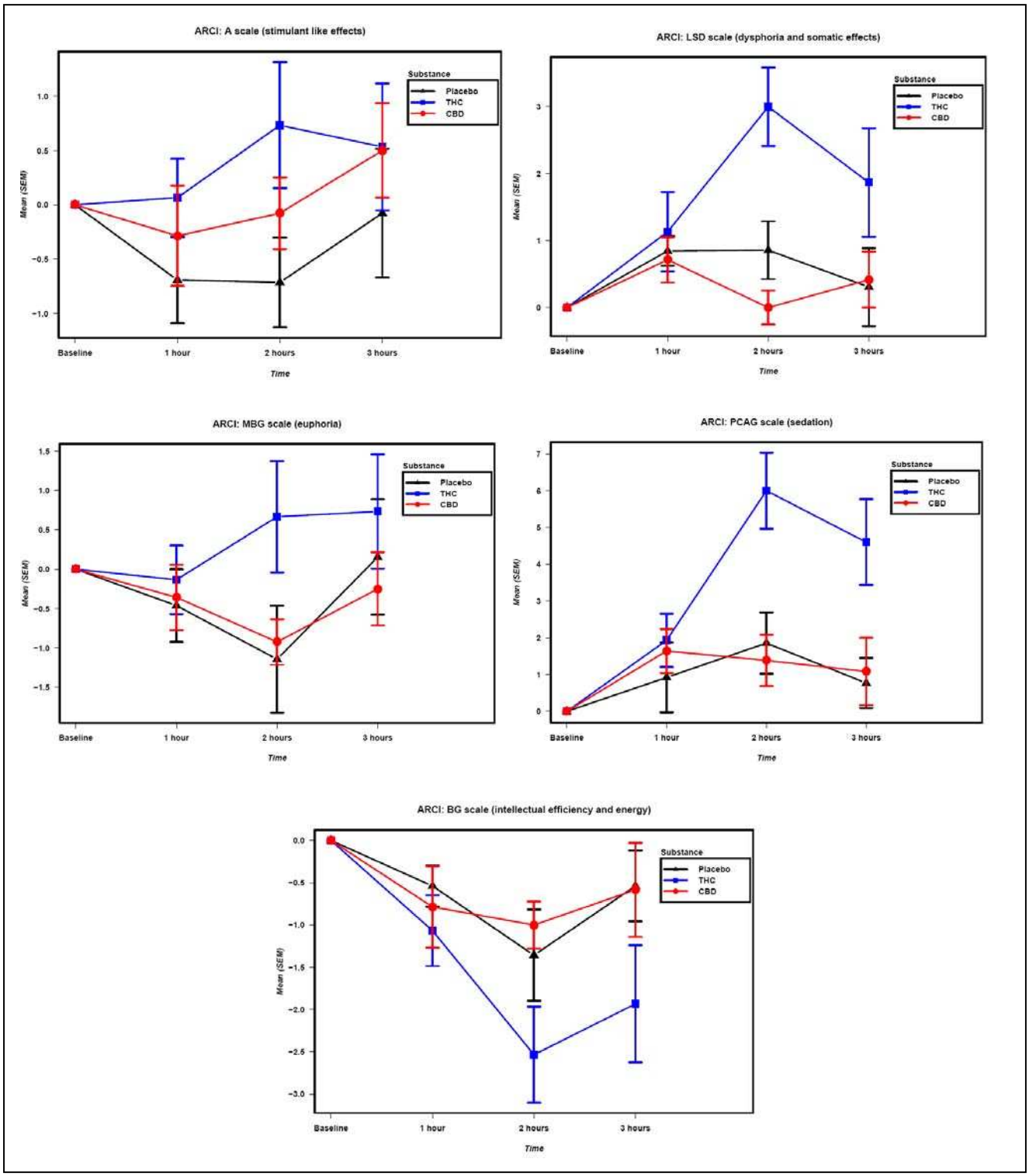

Fig. (3). Changes in subjective symptomatology related to drug intoxication: stimulant effects, induced euphoria, dysphoria, intellectual efficiency and sedation (ARCI) scores after administration of 10 mg THC, 600 mg CBD, and placebo. The figure shows mean (±SEM) values

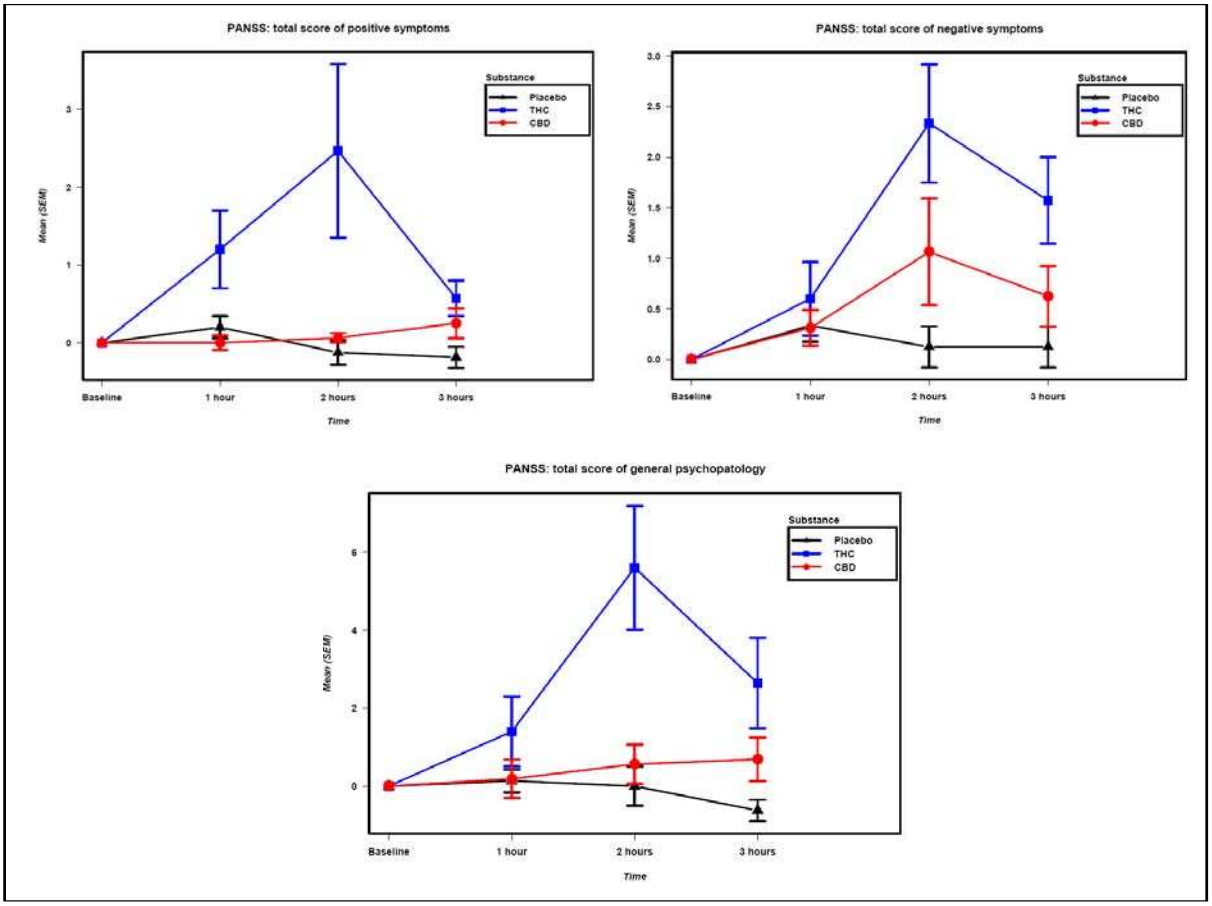

Fig. (4). Changes from baseline over time in positive and negative psychotic symtomatology and total score of general psychopatology of PANNS after administration of THC, CBD, and placebo. The figure shows mean (±SEM) values.

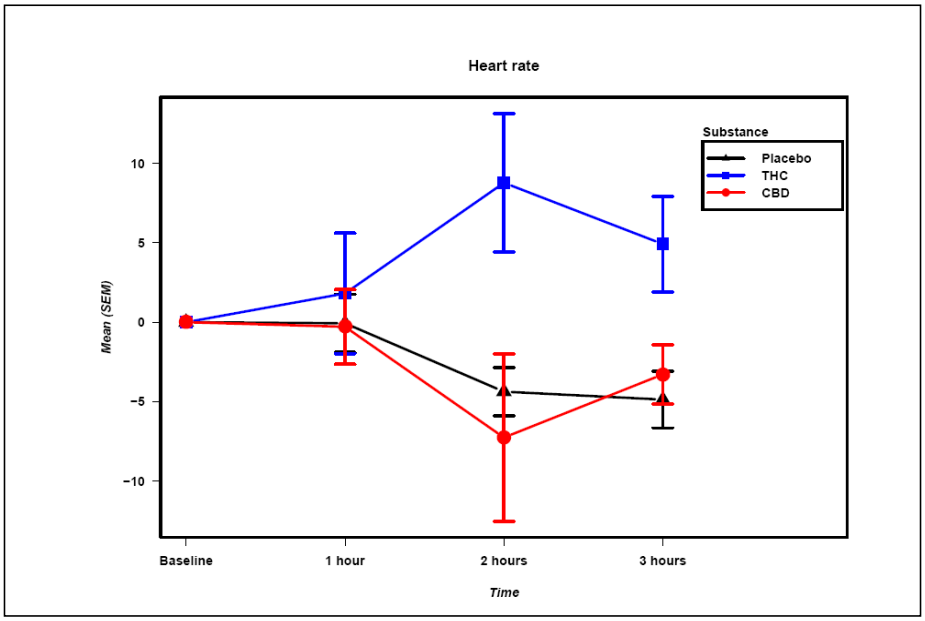

Fig. (5). Changes from baseline over time in heart rate after oral administration of 10 mg of THC, 600 mg of CBD, and placebo. Figure shows mean (+SEM) values.

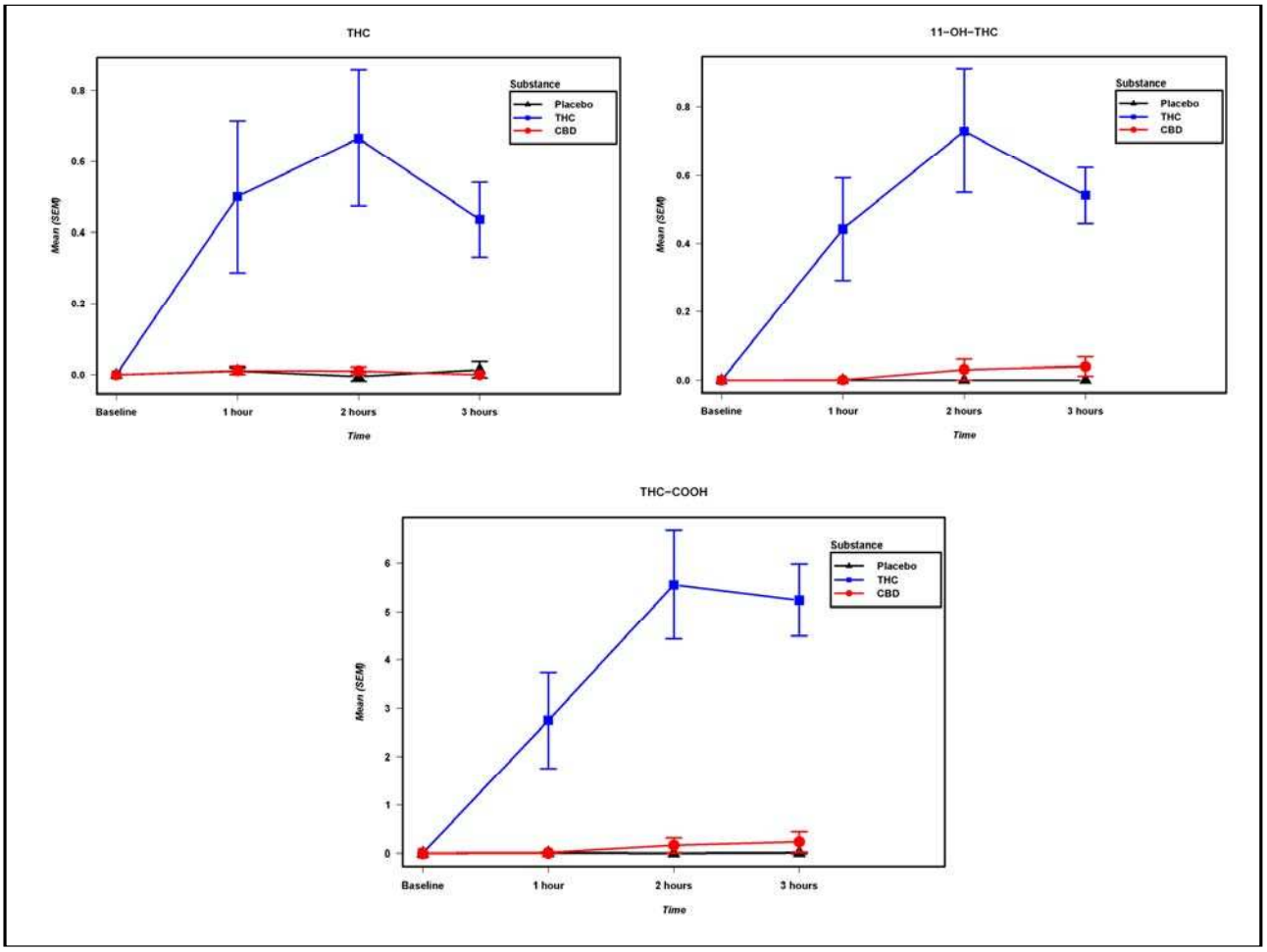

Fig. (6). Time course of THC, 11-OH-THC and THC-COOH whole blood levels after oral administration of 10 mg of THC, 600 mg of CBD, and placebo. Figure shows mean (±SEM) values.

Table 3. Results of Physiological Effects Comparisons after a Single Oral dose of Placebo, THC, CBD and Placebo Administration with Respect to the Area Under the Curve (AUC) and Effect at 2 Hours

	AUC				Effect at 2 hours			
Physiological parameters	**F**	**p**		**p***	**F**	**p**		**p***
Systolic blood pressure	0.96	0.397			1.17	0.327		
Diastolic blood pressure	0.27	0.769			2.44	0.07		
Heart rate	4.72	0.019	1	0.010	4.83	0.016	1	0.049
			2	0.924			2	0.859
			3	0.037			3	0.013

*Pair wise comparisons: 1) placebo vs. THC, 2) placebo vs. CBD, and 3) THC vs. CBD

Whole Blood Drug Concentration Levels

Although some previous studies have reported that THC plasma concentrations were out of phase with its behavioural, cognitive or endocrine effects [61,62, 81, 82], we found that the level of subjective intoxication (ASI) and the severity of positive and negative total score (PANSS-TS) correlated with whole blood levels of 11-OH-THC at 1 hour post drug administration, and with the levels of THC at 3 hours post drug administration.

Limitations

Some methodological limitations of this study need to be noted. First, we used a within-subject cross-over design, which minimised the confounding of effects of inter-subject differences, but was logistically demanding, limited the total number of participants that could be studied. In an effort to minimise the potentially confounding effects of previous substance use, we restricted inclusion to volunteers who has taken cannabis less than 15 times in their life-

time, with none in the last month. However, for ethical reasons, it was not possible to study participants who were completely cannabis naïve. The subjective effects of cannabis may be greater at the first time of use [11, 17], so we might have observed different results in a sample with more experience with cannabis. In the systematic review we observed that one of the three subjects, a women, who presented acute psychotic symptoms was from a study in naïve subjects [48] (Table **1**). The dose of THC chosen for this study (10mg) was designed to be comparable to that delivered from a typical cannabis cigarette, and it is possible that had we used a higher dose, effects on cognitive performance may have been more evident.

In summary, the data from the present study suggest that a single dose of THC, comparable to that delivered form a cannabis cigarette, had significant acute symptomatic and physiological effects in healthy volunteers. Moreover, CBD has confirmed to be safe and well-tolerated in humans as previously observed [25].

CONFLICTS OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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