Original Paper

The effect of five day dosing with THCV on THC-induced cognitive, psychological and physiological effects in healthy male human volunteers: A placebo-controlled, double-blind, crossover pilot trial

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Amir Englund, Zerrin Atakan, Aleksandra Kralj, Nigel Tunstall, Robin Murray and Paul Morrison

Abstract

Rationale: Cannabis is mostly grown under illegal and unregulated circumstances, which seems to favour a product increasingly high in its main cannabinoid Δ-9-tetrahydrocannabinol (THC). Δ-9-tetrahydrocannabivarin (THCV) is a relatively untested cannabinoid which is said to be a cannabinoid receptor neutral antagonist, and may inhibit the effects of THC.

Objectives: To explore the safety and tolerability of repeated THCV administration and its effects on symptoms normally induced by THC in a sample of healthy volunteers.

Methods: Ten male cannabis users (<25 use occasions) were recruited for this within-subjects, placebo-controlled, double-blind, cross-over pilot study. 10mg oral pure THCV or placebo were administered daily for five days, followed by 1mg intravenous THC on the fifth day.

Results: THCV was well tolerated and subjectively indistinguishable from placebo. THC did not significantly increase psychotic symptoms, paranoia or impair short-term memory, while still producing significant intoxicating effects. Delayed verbal recall was impaired by THC and only occurred under placebo condition (Z=-2.201, p=0.028), suggesting a protective effect of THCV. THCV also inhibited THC-induced increased heart rate (Z=-2.193, p=0.028). Nine out of ten participants reported THC under THCV condition (compared to placebo) to be subjectively weaker or less intense (χ^2=6.4, p=0.011). THCV in combination with THC significantly increased memory intrusions (Z=-2.155, p=0.031).

Conclusion: In this first study of THC and THCV, THCV inhibited some of the well-known effects of THC, while potentiating others. These findings need to be interpreted with caution due to a small sample size and lack of THC-induced psychotomimetic and memory-impairing effect, probably owing to the choice of dose.

Keywords

THCV, THC, Δ9-tetrahydrocannabivarin, Δ9-tetrahydrocannabinol, cannabis, memory, psychosis, cannabinoid, human

Introduction

The effects of cannabis are highly dependent upon the various amounts of the different active components of the plant, the cannabinoids (Englund et al., 2013; Morgan et al., 2010; Schubart et al., 2011; Zuardi et al., 1982). The *Cannabis Sativa* L. plant produces over 100 different cannabinoids (Hanus, 2009). Each cannabinoid is produced in various concentrations, depending mostly on the specific genetic make-up of the individual strain, but also factors such as degrees of lighting, temperature and nutrition (Potter, 2014). The main active component of cannabis is Δ9-tetrahydrocannabinol (THC), which is the most abundant cannabinoid produced by the plant, while the second most common is cannabidiol (CBD) (Potter, 2014). A lesser common cannabinoid is Δ9-tetrahydrocannabivarin (THCV), which often exists in very low quantities in most cannabis varieties (Mehmedic et al., 2010). However, certain strains of cannabis have been identified which are particularly rich in THCV (Hillig and Mahlberg, 2004).

Hollister and colleagues were the first to administer pure THCV to six healthy volunteers. The participants received an intravenous (IV) dose of 7mg THCV (Hollister, 1974). One of the participants noticed no effects, while the others reported mild to moderate cannabis-like effects. The authors concluded that THCV is roughly 25% as psychoactive as THC. THCV was initially thought to be an agonist, albeit weak, at the CB1 receptor as previous animal studies had indicated (Gill et al., 1970). A more recent study on mice highlighted this by demonstrating that the increased tolerance to pain produced by THCV was inhibited by the known CB1 receptor inverse agonist SR141716A (Rimonabant) (Pertwee et al., 2007). Although it seems as if THCV functions as a CB1

Department of Psychosis Studies, Institute of Psychiatry, King's College London, London, UK

Corresponding author:
Amir Englund, Institute of Psychiatry, King's College London, 16 De Crespigny Park, SE5 8AF, London, UK.
Email: amir.englund@kcl.ac.uk

agonist, there is also evidence that it acts as a CB1 and CB2 antagonist at lower doses (Thomas et al., 2005). Furthermore, THCV has been shown to inhibit the effects of THC in mice (Pertwee et al., 2007), while not exhibiting characteristics of a CB1 inverse agonist (Rock et al., 2013). This led researchers to conclude that THCV is a CB1 receptor neutral antagonist (Wargent et al., 2013). A neutral antagonist is a compound which binds to a receptor but has 0% efficacy, as opposed to an agonist which has at least some efficacy, or an inverse agonist, which lowers the baseline cellular activity.

A recent systematic review strengthened this notion as it found that three out of four efficacy studies were consistent with THCV as a neutral antagonist, while the fourth found it to be more similar to an inverse agonist (McPartland et al., 2015). Although the precise pharmacodynamic profile of THCV has not yet been fully elucidated, it appears most likely that it acts as a neutral antagonist in the lower dose-ranges, while possibly acting as an agonist at higher doses. However, the notion of THCV as an agonist at higher doses needs replication, as it is merely based on a small sample (Hollister, 1974).

There remains concern regarding blockade of CB1 receptors in the central nervous system, as this has been linked to unfavourable psychiatric side effects. Rimonabant, which is a CB1 receptor inverse agonist, was marketed as an anti-obesity drug and showed very promising results. A meta-analysis found that Rimonabant significantly reduced weight (mean 4.7kg over 12 months), waist circumference and improved cholesterol values (Christensen et al., 2007). However, due to concerns regarding significant increase of anxiety, depression and suicidal ideation in the patients treated with Rimonabant, the drug was withdrawn from the market (Nissen et al., 2008). More recently, studies with Rimonabant in healthy volunteers have shown it to produce a bias towards remembering negatively loaded words (Horder et al., 2012), and increasing anxiety during a public speaking task (Bergamaschi et al., 2014). CB1 antagonists have also shown some indication of improving memory functioning in animals (Lichtman, 2000; Shiflett et al., 2004; Terranova et al., 1996), although this has not yet been observed in humans (Boggs et al., 2012; Horder et al., 2009).

It has been previously demonstrated that an acute administration of a high dose THC can provoke schizophrenia-like psychotic symptoms and cognitive impairment in roughly 40%–50% of healthy volunteers (D'Souza et al., 2004; Morrison et al., 2009). Furthermore, CBD has been shown to protect against the psychotogenic effects of THC (Englund et al., 2013; Schubart et al., 2011). Morgan and colleagues also showed that stronger strains of cannabis with less CBD have a greater negative impact on memory function (Morgan et al., 2010). There is evidence from a recent study in rats that THCV is anti-psychotic in a phencyclidine model of psychosis to a similar degree as clozapine (Cascio et al., 2015). However, it remains unknown if THCV has similar protective properties in humans as does CBD. In this small pilot study, we report the findings of five days dosing with THCV followed by IV administration of THC in ten healthy male volunteers. We hypothesize that THCV will be well tolerated and inhibit the cognitive, psychological and physiological effects of THC.

Methods

The study was approved by the Camden and Islington National Research Ethics Committee. All subjects were given time to study the participation sheet, and provided written informed consent. The safety of IV THC administrations has been previously reviewed (Carbuto et al., 2012). Participants were informed of the possibility of short-lived anxious and psychotic like effects of IV THC, and were made aware of stopping procedures of the study as well as the possibility of receiving rescue medication (Lorazepam 1–4mg).

Design

This was a randomized, double-blind, placebo-controlled, cross-over study in which participants were dosed for five days with THCV or identical placebo capsules, before administration of IV THC. A minimum of two-weeks wash-out period was allowed between each testing week. Consent and screening of participants were carried out on a separate occasion prior to the first testing week. The testing weeks consisted of baseline assessment on a Monday, which followed administration of either THCV or placebo. Participants then returned on Tuesday (Day 2), Wednesday (Day 3) and Thursday (Day 4) for additional dosing and monitoring of potential side-effects. The Friday session started with administration of the final dose of THCV or placebo, followed by post-capsule testing, IV THC administration (1h post-capsule) and post-THC testing (Figure 1 and Table.1). Participants were made aware prior to study enrolment that they would receive THC on each of the Friday sessions, but that the capsules they would take throughout the week would be the same and either placebo or THCV. Participants were informed that they were unlikely to feel any different while taking THCV as this is what preliminary data for this dose indicated (unpublished data on file at GW Pharmaceuticals). However, they were made aware of safety protocols and provided with a 24h emergency number for the study physician. All participants provided a clean urine drugs screen at the start of each testing week, but not at the day of the experiment, as this would test positive to metabolites of THCV and unblind the researcher. Vital signs were tested on every visit.

Participants

Ten healthy male volunteers were recruited for this pilot study by means of recruitment emails sent to staff and students of King's College London. Participants aged between 21 and 35, with a minimum lifetime cannabis use of at least once and no more than 25 times were invited for screening and consent. Exclusion criterion included a history of mental illness (psychotic disorder, depression, anxiety), major mental illness in first-degree family member (e.g. schizophrenia), major physical illness, previous treatment with psychotropic medications, past or present drug and alcohol dependence (excluding nicotine) and being unable or unwilling to give written informed consent. All participants provided written informed consent. Participant demographics are presented in Table.2.

Pharmaceuticals and pharmacokinetics

THCV (2×5mg capsules) and placebo were provided by GW Pharmaceuticals UK. Synthetic THC was acquired from STI Pharmaceuticals UK, via THC Pharm GmbH (Frankfurt am Main, Germany) and prepared as 1mg/mL vials (diluted in ethanol) for IV injection, by Bichsel Laboratories (Interlaken, Switzerland) as

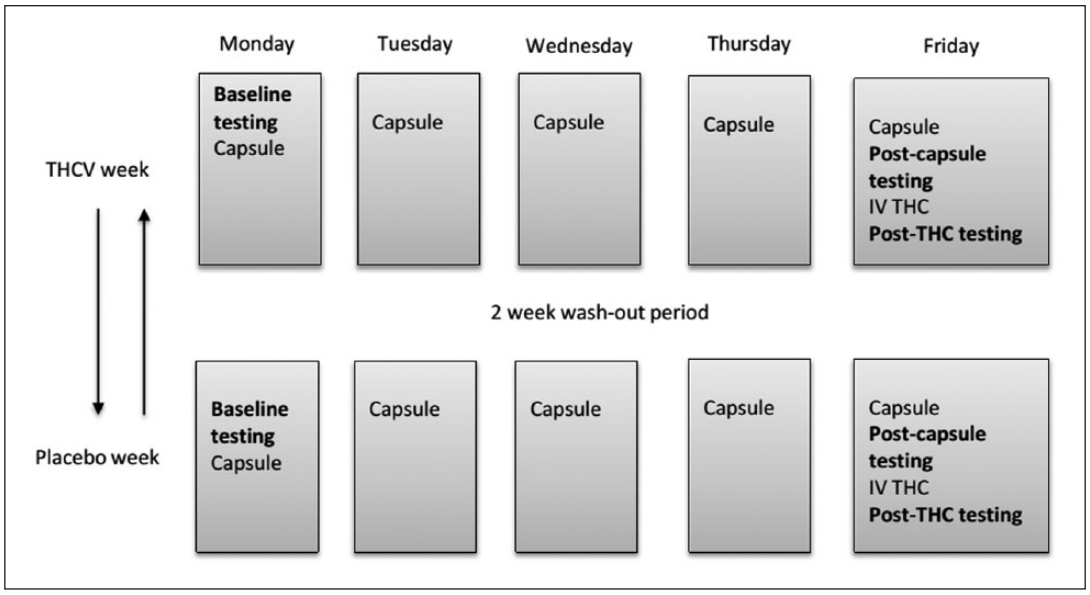

Figure 1. The time-line of the experimental weeks. The order of assignment to placebo or THCV treatment was randomized.

Table 1. Time-line of experimental session.

Time (hours)	Experimental day
0h 00min	Baseline blood sample, oral THCV/ placebo administration
0h 10min – 0h 25min	Cognitive testing (HVLT, digit span)
0h 25min – 0h 55min	Psychological assessments (CAPE, SSPS, UMACL, BAI, VAS)
1h 00min – 1h 10min	IV THC administration
1h 15min	5min post-THC blood sample
1h 25min	15min post-THC blood sample
1h 30min – 1h 45min	Cognitive testing (HVLT, digit span)
1h 45min – 2h 15min	Psychological assessments (CAPE, SSPS, UMACL, BAI, VAS)
2h 10min	1h post-THC blood sample
3h 30min – 5h 00min	Discharge (depending on clinician assessment of sobriety)

THCV: Δ9-tetrahydrocannabivarin; IV THC: intravenous Δ9-tetrahydrocannabinol; HVLT: Hopkins Verbal Learning Task; CAPE: Community Assessment of Psychic Experiences; SSPS: State Social Paranoia Scale; UMACL: the University of Wales Mood Adjective Checklist; BAI: Beck's Anxiety Inventory; VAS: visual analogue scale.

Table 2. Participant demographics.

No. participants	10
Age (mean (range))	23.8 (21–33)
Handedness	2 left handed
BMI (mean (range))	22.69 (18-27.4)
Education	4 college degree, 6 university degree
Cannabis	
Use status	7 past users
Age of first use (mean (range))	18.6 (16–27)
Lifetime use occasions (mean (range))	12.9 (3–25)
Other drug exposure	**No. of participants**
Tobacco	8
Alcohol (mean units/week, range)	10 (9, 2–20)
Amphetamine	1
LSD	3
Ketamine	2
Psilocybin	2
MDMA	4
Mephedrone	2
Cocaine	4
Nitrous oxide	1
2-CB	1

previously described (Naef et al., 2004). Intravenous THC was prepared as a solution containing 9ml normal saline and 1ml THC. THC was administered over 10 minutes with 1ml/min pulses (total dose 1mg). Oral THCV (10mg) was administered each day for five days in the hope of reaching steady state plasma concentration of THCV at the time of THC administration. This dose was chosen based on recommendations and limited unpublished data on file at GW Pharmaceuticals on a formulation with a 5:1 THCV/THC ratio, in which 10mg was the highest dose that was well-tolerated with no significant side-effects. For this study we chose a slightly lower dose of IV THC compared to our previous studies (Englund et al., 2013; Morrison et al., 2009, 2011; Stone et al., 2012), to better highlight the possible inhibitory effects of THCV in case they are easily overpowered by a high THC dose. Blood samples to measure plasma cannabinoid levels were taken prior to the administration of the final oral tablet (baseline), followed by 5min, 15min and 1h after the end of IV THC infusion. Plasma cannabinoid levels were analysed at Quotient Bioresearch (Cambridgeshire UK), where ultra performance liquid chromatography–tandem mass spectrometry was used for quantification of THC, THCV, 11-OH-THC and 11-OH-THCV. The lower limit of quantification was 0.25ng/ml and the upper limit of quantification was 250ng/ml.

Cognitive tasks

The Hopkins Verbal Learning Task – Revised. The Hopkins Verbal Learning Task – Revised (HVLT) is a part of the MATRICS Consensus Cognitive Battery (PAR, Inc FL 33549). It consists of learning a list of 12 words across three trials (nouns from three taxonomic categories), followed by recall 20–25 minutes later, of which there are five validated versions. The versions were randomized between each participant, and version 1 was used for both baseline testing points. The HVLT tests the participants' performance on immediate and delayed recall, as well as intrusions and repetitions. Immediate recall is measured as the total number of words recalled during the three learning trials. Delayed recall is measured as the percentage of correctly recalled words compared to the best trial from the learning phase. Repetitions refer to number of times a correctly recalled word is repeated, and intrusions are words recalled that are related to the words in the list, yet not part of the original list.

Digit span. The digit span refers to the longest list of numbers the participant can correctly recall, both in forward and backward order. The task starts at the length of four digits and is increased by one digit for each successful trial. The task is ended when the participant fails to give the correct order after two consecutive attempts.

Psychological scales

Community Assessment of Psychic Experiences-state (CAPE-state). The CAPE-state is a 42-item validated scale which measures positive, negative and depressive dimensions of psychotic-like experiences (Stefanis et al., 2002), where each item has a yes/no response option. When a yes response has been given, the participant is asked to rate on a four-point scale how distressing the experience was to them. This version of the CAPE produces a frequency score and a distress score for each of the different symptom dimensions.

State Social Paranoia Scale (SSPS). The SSPS is a ten-item instrument which measures persecutory thoughts (Freeman et al., 2007). The persecutory items (e.g. 'someone had bad intentions towards me') are presented among ten neutral items and scored on a five-point scale (do not agree – totally agree).

The University of Wales Mood Adjective Checklist (UMACL). The UMACL is used to measure the three major dimensions of affect (Matthews et al., 1990): Hedonic tone (pleasure–displeasure), Energetic arousal (awake–tiredness), and Tense arousal (tension–relaxation). Each dimension consists of four negative and four positive adjectives, which the participant scores on a four-point scale. The scores for each dimension are then added up, and range from -12 to 12. The UMACL was used at each study visit, including dosing visits, to measure potential THCV related mood changes.

Beck's Anxiety Inventory. The Beck's Anxiety Inventory measures clinical symptoms of anxiety and consists of 20-items scaled on a four-point scale (Not at all – Severely) (Beck et al., 1988).

Table 3. Effects of THCV and placebo, presented as occasions among all participants.

	Placebo	THCV
Tired	1	3
Trouble falling asleep	0	1
Nausea	0	1
Feeling active	2	0
Stiff neck/shoulder	2	0
Increased creativity	1	1

Visual analogue scale (VAS). Visual analogue scales were used to measure the following feeling states: 'high', 'calm and relaxed', 'tired', 'anxious' and 'stoned'. The scale consists of a 100mm horizontal line on which the participant makes a vertical mark indicating how much of the feeling state he/she is experiencing, ranging from 'Not at all' to 'As much as could possibly be'.

Subjective effects. The pleasurable effects of the drugs were measured on a five-point Likert scale from 'no' to 'extreme' on the item 'This experience is pleasurable'. This was measured at baseline, post-capsule, and post-THC. After the completion of the second experimental session, the participants were asked to name which one of the two THC-occasions they felt were the weakest or least intense.

Statistical analyses

All analyses were performed in SPSS 21 (IBM, NY). Due to the small sample size of this study none of the data were normally distributed, Friedman's non-parametric repeated measures analysis of variance (ANOVA) was used to analyse differences between treatment weeks (1. THCV, 2. Placebo) across the testing points (1. Baseline, 2. Post-capsule, 3. Post-THC). Certain measures included more time points (UMACL, blood pressure, heart rate and plasma cannabinoids). Wilcoxon signed-rank test was used for post hoc analyses where significant main effects were found. Planned comparisons were performed where notable differences in mean scores were found. Significance was accepted at $p<0.05$, and all comparisons were two-tailed.

Results

At the end of the study six out of ten participants correctly guessed which week they had been given the THCV capsules ($\chi^2=0.4$, $p=0.527$), indicating THCV to be indistinguishable from placebo. Table 3 lists self-reported effects of study participants while taking either placebo or THCV during the study weeks. No order effects were found. All results and corresponding χ^2-statistic are presented in Table 4.

Pharmacokinetics

All participants were negative for THC and 11-OH-THC for each of the experimental sessions by means of plasma analysis. There were no significant differences between placebo and THCV conditions in THC concentrations at 5min post-THC ($Z=-1.355$, $p=0.176$)

Table 4. Mean, median, SD, range and Friedman's χ^2 for all measures at all study time points.

				Baseline	Post-capsule	Post-THC	Friedman's χ^2
				Mean (median), SD (min–max)	*Mean (median), SD (min–max)*	*Mean (median), SD (min–max)*	χ^2 *(p-value)*
Cognition							
HVLT		Immediate	Placebo	31.8 (32), 3.2 (25–36)	30.7 (31.5), 2.6 (27–34)	30.6 (32), 3.6 (24–35)	4.9 (0.086)
			THCV	30.6 (30.5), 2.9 (26–36)	31.7 (33), 3.4 (24–35)	30.4 (31.5), 3.1 (25–34)	1.94 (0.38)
		Delayed	Placebo	94.6 (91.7), 4.7 (89–100)	96.7 (100), 9.6 (82–110)	78.5 (83.3), 20.6 (36–100)	**7.44 (0.024)**
			THCV	97.3 (100), 4.3 (90–100)	95 (100), 7 (83–100)	90.2 (91.7), 12.8 (67–111)	4.33 (0.115)
		Repetitions	Placebo	1.4 (0), 2.3 (0–6)	1.5 (0.5), 2.1 (0–6)	0.8 (0.5), 1.2 (0–4)	0.78 (0.678)
			THCV	0.7 (0.5), 0.8 (0–2)	0.8 (0), 1.6 (0–5)	1 (0), 1.5 (0–4)	0.26 (0.878)
		Intrusions	Placebo	0.9 (0), 1.9 (0–6)	1.1 (0.5), 1.4 (0–4)	0.5 (0), 1.1 (0–3)	0.92 (0.63)
			THCV	0.3 (0), 0.5 (0–1)	0.2 (0), 0.6 (0–2)	2.4 (2), 2.2 (0–7)	**8.6 (0.014)**
Digit-span		Forward	Placebo	7.2 (7), 1.5 (5–9)	7.4 (7), 1.2 (6–10)	6.9 (7), 1 (6–9)	1.75 (0.417)
			THCV	7.6 (7), 1 (7–10)	7.7 (7), 1.5 (6–10)	7.1 (7), 1 (5–8)	1.74 (0.419)
		Reverse	Placebo	6 (6), 1.6 (4–9)	6 (6), 1.1 (4–7)	5.6 (5), 1.2 (4–8)	0.77 (0.679)
			THCV	5.6 (6), 0.8 (4–7)	6.7 (7), 1.3 (5–9)	5.6 (5.5), 1 (4–7)	**6.75 (0.034)**
Psychology							
CAPE	Positive sym.	Frequency	Placebo	0.3 (0), 0.7 (0–2)	0 (0), 0 (0–0)	0.4 (0), 0.5 (0–1)	4 (0.135)
			THCV	0.1 (0), 0.3 (0–1)	0 (0), 0 (0–0)	0.3 (0), 0.7 (0–2)	2 (0.368)
		Distress	Placebo	0.1 (0), 0.3 (0–1)	0 (0), 0 (0–0)	0.3 (0), 0.9 (0–3)	1 (0.607)
			THCV	0 (0), 0 (0–0)	0 (0), 0 (0–0)	0 (0), 0 (0–0)	–
	Negative sym.	Frequency	Placebo	0.4 (0), 1 (0–3)	0.2 (0), 0.4 (0–1)	2.4 (2), 2.5 (0–8)	**8.72 (0.013)**
			THCV	0.6 (0), 1.3 (0–4)	0.1 (0), 0.3 (0–1)	2.8 (3), 2 (0–6)	**13.13 (<0.001)**
		Distress	Placebo	0.1 (0), 0.3 (0–1)	0 (0), 0 (0–0)	0.5 (0), 1.6 (0–5)	1 (0.607)
			THCV	0 (0), 0 (0–0)	0 (0), 0 (0–0)	0.2 (0), 0.4 (0–1)	4 (0.135)
	Depressive sym.	Frequency	Placebo	0 (0), 0 (0–0)	0.1 (0), 0.3 (0–1)	0.3 (0), 0.9 (0–3)	1 (0.607)
			THCV	0 (0), 0 (0–0)	0.2 (0), 0.4 (0–1)	0 (0), 0 (0–0)	4 (0.135)
		Distress	Placebo	0 (0), 0 (0–0)	0 (0), 0 (0–0)	0.5 (0), 1.6 (0–5)	2 (0.368)
			THCV	0 (0), 0 (0–0)	0.1 (0), 0.3 (0–1)	0 (0), 0 (0–0)	2 (0.368)

(Continued)

Table 4. (Continued)

			Baseline	Post-capsule	Post-THC	Friedman's χ^2
			Mean (median), SD (min–max)	*Mean (median), SD (min–max)*	*Mean (median), SD (min–max)*	χ^2 *(p-value)*
SSPS		Placebo	10.10 (10), 0.3 (10–11)	10.10 (10), 0.3 (10–11)	10.9 (10), 2.5 (10–18)	0.67 (0.717)
		THCV	10.10 (10), 0.3 (10–11)	10.20 (10), 0.4 (10–11)	10 (10), 0 (10–10)	3 (0.223)
BAI		Placebo	0.7 (0.5), 0.9 (0–3)	1 (0), 1.5 (0–4)	7.7 (4), 11.2 (1–39)	**15.17 (<0.001)**
		THCV	0.7 (1), 0.7 (0–2)	2.8 (1), 6.2 (0–20)	5.6 (5.5), 2.9 (1–11)	**12.97 (0.002)**
VAS	Anxious	Placebo	7.8 (6.5), 6.3 (0–23)	11.9 (10), 9.2 (0–26)	18.8 (8.5), 26.8 (0–88)	0.72 (0.697)
		THCV	10.2 (3.5), 13.2 (0–32)	21.3 (18), 21 (0–68)	10.9 (8), 11.7 (0–37)	2.39 (0.303)
	Calm	Placebo	72.5 (74), 12.2 (55–92)	69.4 (70), 14.5 (53–100)	68.2 (79.5), 26.7 (1–90)	0.0 (>0.999)
		THCV	64.9 (62), 15 (40–91)	59.2 (60.5), 24.5 (9–94)	64.7 (71.5), 20.1 (27–89)	1.8 (0.407)
	Tired	Placebo	21.2 (19.5), 15.8 (0–52)	19.7 (19), 19.8 (0–62)	34.5 (34.5), 19.7 (0–66)	2.89 (0.236)
		THCV	16.1 (12.5), 14 (0–38)	25.6 (14), 25.1 (0–64)	42.8 (41), 26.9 (2–86)	4.2 (0.122)
	High	Placebo	36.2 (31.5), 29 (3–82)	24.6 (13), 27 (0–67)	53 (57.5), 26 (2–84)	**7.74 (0.021)**
		THCV	22.1 (8), 28 (0–76)	15.3 (7), 23 (0–66)	57.6 (52.5), 15 (39–80)	5.68 (0.058)
	Stoned	Placebo	1.4 (0.5), 2.2 (0–7)	7.1 (3), 12.2 (0–40)	42.9 (46.5), 22.6 (5–75)	**15.94 (<0.001)**
		THCV	5.8 (3), 6.9 (0–20)	9.9 (2.5), 20.5 (0–67)	43 (41), 22.5 (14–76)	**10.43 (0.005)**
Subjective	Pleasure	Placebo	1.1 (1.5), 0.31 (0–2)	0.5 (0), 0.22 (0–2)	1.7 (2), (0–3)	5.4 (0.067)
		THCV	1.2 (1), 0.33 (0–3)	0.7 (0.5), 0.26 (0–2)	1.6 (1.5), 0.31 (0–3)	**7.16 (0.028)**

		Baseline	5min post-THC	15min post-THC	1h post-THC	Friedman's χ^2
		Mean (median), SEM (min–max)	*Mean (median), SEM (min–max)*	*Mean (median), SEM (min–max)*	*Mean (median), SEM (min–max)*	χ^2 *(p-value)*
Plasma						
THC (ng/mL)	Placebo	0 (0), 0 (0–0)	14.2 (14.9), 3.9 (7.5–18.8)	4.9 (5.1), 0.9 (3.6–6.1)	2.2 (2.4), 0.4 (1.5–2.7)	**24 (<0.001)**
	THCV	0 (0), 0 (0–0)	11.53 (11.45), 2.7 (7.37–16)	4.44 (4.32), 0.5 (3.8–5.69)	2.09 (2.04), 0.2 (1.85–2.41)	**21 (<0.001)**
11-OH-THC (ng/mL)	Placebo	0 (0), 0 (0–0)	1.2 (1), 0.7 (0.6–2.9)	0.9 (0.8), 0.4 (0.6–1.9)	0.7 (0.6), 0.2 (0.5–1.1)	**25.9 (<0.001)**
	THCV	0 (0), 0 (0–0)	1.1 (1.1), 0.2 (0.7–1.5)	0.9 (0.9), 0.3 (0.6–1.4)	0.6 (0.6), 0.2 (0.4–1)	**22.95 (<0.001)**

Table 4. (Continued)

			Baseline	Day 2	Day 3	Day 4	Post-capsule	Post-THC	Friedman's χ^2
			Mean (median),SEM (min–max)	*Mean (median), SEM (min–max)*	*Mean (median), SEM (min–max)*	*Mean (median), SEM (min–max)*	*Mean (median), SEM (min–max)*	*Mean (median), SEM (min–max)*	*χ^2 (p-value)*
Psychology									
UMACL	Hedonic tone	Placebo	9.3 (9.5), 2.1 (6–12)	10.4 (11.5), 2 (7–12)	9.8 (11), 2.8 (4–12)	9.4 (10.5), 3 (4–12)	9.4 (10.5), 2.9 (5–12)	8.4 (10), 6.2 ((−9)–12)	6.1 (0.3)
		THCV	8.4 (8), 1.8 (6–12)	10.1 (11), 2.3 (6–12)	10.5 (11.5), 1.9 (7–12)	9.7 (11.5), 3 (4–12)	9.4 (10.5), 2.9 (5–12)	9.7 (9.5), 1.9 (7–12)	**11.2 (0.048)**
	Energetic arousal	Placebo	4.9 (6), 4.5 ((−5)–9)	7.2 (7.5), 1.8 (5–10)	6.7 (5.5), 3.1 (2–11)	7.9 (8.5), 2.6 (3–11)	6 (6), 3.4 ((−1)–11)	3.7 (3.5), 5.2 ((−5)–11)	6.1 (0.298)
		THCV	5.2 (4), 2.9 (1–10)	6.8 (7.5), 2.7 (3–11)	6.7 (8.5), 3.7 ((−1)–10)	6.6 (8), 4 (1–11)	4.6 (4), 3.9 ((−1)–11)	0.7 (0), 5 ((−5)–10)	**15.1 (0.01)**
	Tense arousal	Placebo	−9 (−9), 2.2 ((−12)–(−6))	−9.4 (−10.5), 3 ((−12)–(−4))	−9.4 (−9), 2.1 ((−12)–(−6))	−9.4 (−10.5), 3 ((−12)–(−3))	−8.1 (−9), 4 ((−12)–(−1))	−6.5 (−9), 5.7 ((−11)–7)	3.85 (0.571)
		THCV	−7.3 (−7), 2.9 ((−12)–(−4))	−7.8 (−7.5), 3.8 ((−12)–(−2))	−9 (−9.5), 2.8 ((−12)–(−3))	−9.6 (−10.5), 2.6 ((−12)–(−4))	−6.6 (−7), 3.6 ((−11)–1)	−7.2 (−8), 3.3 ((−12)–(−1))	9.09 (0.106)

			Baseline	Day 2	Day 3	Day 4	Post-capsule	15min post-THC	1h post-THC	Discharge	Friedman's χ^2
			Mean (median), SEM (min–max)	*Mean (median), SEM (min–max)*	*Mean (median), SEM (min–max)*	*Mean (median), SEM (min–max)*	*Mean (median), SEM (min–max)*	*Mean (median), SEM (min–max)*	*Mean (median), SEM (min–max)*	*Mean (median), SEM (min–max)*	*χ^2 (p-value)*
Cardiovascular	Heart rate	Placebo	61.4 (59), 10.9 (51–87)	68.6 (66.5), 7 (60–82)	64.8 (64.5), 7.8 (55–77)	67.4 (70.5), 11.9 (53–86)	68.5 (72.5), 11.4 (53–84)	77.7 (77), 14.7 (60–110)	59.4 (58), 10.2 (49–83)	64.2 (60), 10.1 (56–82)	**23.1 (0.002)**
		THCV	59.5 (57), 8.7 (51–80)	66.9 (67.5), 11.2 (50–84)	61.1 (59), 5.9 (54–71)	63.1 (61.5), 9.6 (53–84)	67.1 (63), 11.4 (53–84)	69.6 (66.5), 8.8 (59–84)	64.2 (62.5), 10.5 (50–85)	65.4 (58), 11.5 (55–83)	**14.6 (0.041)**
	Systolic BP	Placebo	139 (136), 13 (116–160)	128 (133), 10 (112–138)	130 (130), 8 (117–145)	128 (128), 6 (114–137)	125 (124), 7 (110–138)	127 (127), 17 (110–167)	131 (128), 9 (121–150)	132 (128), 11 (121–160)	**17.9 (0.012)**
		THCV	136 (139), 14 (115–156)	133 (133), 8 (117–144)	132 (133), 9 (120–149)	130 (124), 14 (113–155)	132 (131), 10 (109–147)	126 (126), 6 (113–136)	130 (129), 12 (117–153)	135 (137), 10 (120–150)	7.8 (0.349)
	Diastolic BP	Placebo	77 (80), 8 (62–88)	72 (71), 7 (66–90)	68 (69), 11 (53–89)	71 (67), 11 (63–97)	70 (69), 5 (63–77)	71 (71), 7 (57–83)	75 (77), 7 (64–85)	70 (69), 9 (58–84)	10.3 (0.172)
		THCV	77 (79), 10 (61–89)	72 (67), 13 (60–102)	71 (71), 5 (64–79)	72 (73), 10 (53–86)	71 (71), 8 (60–84)	71 (70), 9 (61–91)	69 (71), 8 (55–83)	72 (77), 12 (54–82)	1.3 (0.988)

and 1h post-THC (Z=-1.051, p=0.293). There was a weak trend towards higher THC plasma concentrations under placebo condition at the 15min post-THC session (Z=-1.718, p=0.086). Plasma THCV was only above limit of quantification (ALQ, >0.25 ng/mL) in three out of 37 samples, while its metabolite 11-OH-THCV was detectable in 11 out of 37 samples. The five-day dosing regimen of THCV failed to produce steady state levels.

Cognition

Hopkins Verbal Learning Task. There was no significant practice effect of the HVLT version 1 across baseline visits.

Immediate recall: There was no statistically significant change in number of words learned across sessions under both conditions

Post hoc analysis did not show any significant differences between post-capsule and post-THC sessions under THCV (Z=-1.349, p=0.177) or placebo condition (Z=-0.423, p=0.672).

Delayed recall: There was a statistically significant decrease in proportion of words recalled across sessions, but only under placebo condition. Post hoc analysis revealed a significant decrease in words recalled between post-capsule and post-THC session under placebo condition (Z=-2.201, p=0.028), but not under THCV condition (Z=-1.524, p=0.128).

Repetitions: There was no statistically significant change in repetitions across sessions under either condition.

Intrusions: There was a statistically significant increase in intrusions across sessions but only under THCV condition. Post hoc analysis revealed a significant increase between post-capsule and post-THC sessions under THCV condition (Z=-2.155, p=0.031).

Digit-span forward. There was no statistically significant change in numbers recalled across sessions under either condition.

Digit-span reverse. There was a statistically significant change in numbers recalled across sessions but only under THCV condition. Post hoc analysis revealed a significant improvement in reverse digit span performance between baseline and post-capsule and post-THC sessions under THCV condition (Z=-2.050, p=0.04).

Psychology

CAPE-state.

Positive symptoms: There was no statistically significant change in positive symptom frequency or symptom distress scores across sessions under either condition.

Depressive symptoms: There was no statistically significant change in depressive symptom frequency or symptom distress score across sessions under either condition.

Negative symptoms: There was a statistically significant increase in negative symptom frequency across sessions under both conditions. Post hoc analysis revealed significant increases between post-capsule and post-THC sessions under both placebo (Z=-2.328, p=0.02) and THCV conditions (Z=-2.375, p=0.018). There was no significant increase in symptom distress scores across sessions under either condition.

SSPS. There was no statistically significant change in paranoia across sessions under both conditions. One participant displayed an eight-point increase on the SSPS following THC under placebo condition. This coincided with the hospital fire alarm sounding approximately 20 minutes post THC infusion. The participant had no increase in SSPS scores following THC under THCV condition.

UMACL.

Hedonic tone: There was a statistically significant change in hedonic tone scores across sessions but only under THCV condition. There were no significant changes between post-capsule and post-THC sessions under placebo (Z=0, p=1.00) and THCV condition (Z=-0.352, p=0.725).

Energetic arousal: There was a statistically significant change in energetic arousal scores across sessions under THCV condition. Post hoc analysis revealed a significant decrease between post-capsule and post-THC sessions under THCV condition (Z=-1.99, p=0.047), but not under placebo condition (Z=-1.011, p=0.312).

Tense arousal: There was no statistically significant change in tense arousal scores across sessions under either condition.Post hoc analysis revealed a significant increase between baseline and post-capsule session under THCV condition (Z=-2.055, p=0.04), while this was not significant under placebo.

Beck's Anxiety Inventory. There was a statistically significant increase in Beck's anxiety scores across sessions under both conditions. Post hoc analysis revealed a significant increase of anxiety between post-capsule and post-THC sessions under placebo condition (Z=-2.67, p=0.008), while this was not significant under THCV condition (Z=-1.602, p=0.109).

Visual analogue scale.

Anxious: There was no statistically significant change in VAS anxiety scores across sessions under either condition.

Calm: There was no statistically significant change in VAS calm scores across sessions under either condition.

Tired: There was no statistically significant change in VAS tired scores across sessions under either condition.

High: There was a statistically significant increase in VAS high scores across sessions under placebo condition and at trend level under THCV condition.Post hoc analysis did not show any

significant difference between placebo and THCV conditions at the post-THC testing point (Z=-0.153, p=0.878).

Stoned: There was a statistically significant increase in VAS stoned scores across sessions under both conditions. Post hoc analysis did not show any significant difference between placebo and THCV conditions at the post-THC testing point (Z=-0.051, p=0.959).

Cardiovascular

There was a significant change in systolic blood pressure across sessions but only under placebo condition. There were no significant changes across sessions in diastolic blood pressure under either condition. There was a significant change in heart rate across sessions under both conditions. Post-hoc analysis revealed a significant increase in heart rate between post-capsule and THC+15min testing point under placebo condition (Z=-2.09, p=0.037) while this was not significant under THCV condition (Z=-1.129, p=0.259).

Subjective effects

Pleasure. There was a statistically significant increase in pleasure scores across sessions under THCV condition but at the level of trend for placebo. Post hoc analysis did not show any significant difference between placebo and THCV conditions at the post-THC testing point (Z=-0.172, p=0.863).

Subjective impression of THC strength. Nine out of ten participants reported THC as being either weaker or less intense under THCV condition (χ^2=6.4, p=0.011).

Discussion

To our knowledge this is the first study exploring the effects of THCV and THC in healthy volunteers. THCV was well tolerated among the participants, and no serious adverse effects were observed. In fact, participants could not significantly distinguish the THCV capsules from the placebo capsules. However, during the THCV week, three participants reported feeling more tired than usual, while this only occurred for one participant during placebo treatment. However, these interpretations need to be made with caution as only few plasma samples tested positive for THCV.

Cognition

THC produced impairments to delayed recall, although this effect was only present under placebo condition and absent in the presence of THCV. This suggests a protective and antagonistic effect of THCV on THC-induced memory impairment. Interestingly, the low dose of 1mg iv THC did not produce any significant memory impairment on either the HVLT immediate recall or digit span task. These results highlight the previously shown dose–response effects of THC, where certain effects (anxiety, hallucinations) were seen at higher doses but not at lower ones (Naef et al., 2004). It has been proposed that this may either be due to THC acting as a CB1 antagonist at higher doses (Pertwee, 2008), or disruption of endocannabinoid-mediated neuronal firing (Morrison et al., 2011). There was, however, a significant drop in performance on HVLT delayed recall, an effect that was only present under placebo condition following THC. This drop in performance has been well documented in other studies with THC (D'Souza et al., 2005; Morgan et al., 2010), and is protected against by CBD (Englund et al., 2013; Morgan et al., 2010).

Interestingly, we observed a significant increase in intrusions following THC, but only under THCV condition. This effect was not observed under any of the other conditions. However, it remains unclear if this represents impairment of memory, as performance on all other tasks was not affected under these conditions. It may be possible that THCV inhibits some effects of THC while potentiating others, an observation which merits further study.

We also found a small but significant improvement in performance on the reverse digit span task, where THCV improved performance compared to baseline, while this effect was absent during placebo condition. However, due to a small sample size and many plasma samples being negative for THCV, these effects might represent a type 1 error. Therefore, a replication in a larger study is required to confirm these observations.

Psychological effects

Similarly to the effects on cognition, the dose of 1mg iv THC did not produce any significant positive psychotic symptoms or paranoia, as has been previously reported with higher doses of THC (D'Souza et al., 2004, 2008; Englund et al., 2013; Morrison et al., 2009, 2011). Although one participant experienced paranoia following THC (only under placebo condition), this might have been confounded by the fire alarm sounding during the experiment. In a recent review, we argued that past studies with IV THC have administered doses which more reflected an over-intoxication of cannabis, rather than reflecting recreational cannabis use (Englund et al., 2012). The results of the current study are in agreement with this hypothesis. There was a significant increase of negative symptoms on the CAPE scale, regardless of THCV or placebo condition, following THC, something which has been demonstrated with higher doses of THC (Morrison and Stone, 2011). The most endorsed items were 'Do you feel that you are not very animated' and 'Do you feel that you are lacking in energy'. These results are in line with the post THC reduction in UMACL energetic arousal scores in both conditions, and is something that has been observed in other THC studies (Morrison et al., 2009).

An interesting trend which emerged was that of apparent increased anxiety at the post-capsule testing point, only under THCV condition. This was observed in the UMACL tense arousal, while scores tended in the same direction in the Beck's Anxiety Inventory and VAS anxiety. Seen together, these results seem to indicate a potential, yet weak, anxiogenic effect of THCV alone. However, it is important to remember that these observed small increases in anxiety occurred at the post-capsule testing point, which is on the same day as IV THC administration, and that the anticipation of this might provoke anxiety. This is highlighted in the UMACL tense arousal, where there was an increase at post-capsule testing point compared to Day 3 and 4.

However, as this effect is absent under placebo condition, THCV may make participants more sensitive to anxiogenic events or stimuli. It is important to note that previous research into the effects of CB1 antagonists in healthy volunteers have observed no change to subjective mood while showing a significant bias towards negatively loaded words (Horder et al., 2009, 2012). Future research into the potential anxiogenic potential of THCV would benefit from employing such tasks to better observe such subtle changes in mood.

Subjective effects

Following completion of both THC sessions, participants were asked which THC session they felt was the weakest or least intense. Nine out of ten reported the THC session under THCV condition to be the weaker/less intense experience, suggesting THCV has a significant impact on the subjective intensity of IV THC. Furthermore, we asked participants to rate on a four-point scale how pleasurable they perceived the experience. THC significantly increased how pleasurable the experience was, with no difference between placebo and THCV conditions, suggesting that THCV does not impact on the pleasurable effects of THC. However, future studies would benefit from employing more sensitive measures to evaluate these effects.

Cardiovascular and pharmacokinetics

The most common cardiovascular effects of THC in humans are tachycardia, vasodilatation, increased cardiac output and variable changes to blood pressure (Dewey, 1986). In the present study we observed a high variation in both systolic and diastolic blood pressure following IV THC. Some participants became momentarily hypertensive, while others became hypotensive. This observation sheds some doubt on some small but significant differences found in both systolic and diastolic blood pressure. Tachycardia is a more robust effect observed in this study following THC administration. Interestingly, this effect was blocked by THCV, suggesting a pharmacological inhibition of the peripheral heart rate effects of THC.

The main pharmacokinetic finding in this study was that THCV did not significantly change plasma levels of THC, suggesting that THCV may not affect the bioavailability of THC while still producing measureable changes in the effects of THC. Interestingly, there was a trend towards reduced plasma THC levels under THCV conditions at the 15min post-THC time-point, which coincided with the observed inhibitory effect of THCV on THC-induced heart rate increase. Therefore, the notion that THCV reduces the bioavailability of THC cannot be firmly ruled out. A larger study would be needed to clarify whether the observed THCV effect on heart rate is due to lower levels of plasma THC.

Strangely, only three out of 37 plasma samples showed THCV levels above quantification. This might be due to rapid redistribution of THCV, poor oral absorption, the timing of capsule administration and plasma sampling, the lower limit of quantification (0.25 ng/ml) being set too high or the dose of THCV being too low. The latter alternative may be unlikely, as a recent fMRI study found 10mg oral THCV to produce significant changes to aversive and rewarding stimuli compared to placebo in healthy volunteers (Tudge et al., 2014). We did, however, observe significantly more samples showing quantifiable levels of the THCV metabolite 11-OH-THCV (11 out of 37 samples), indicating the recent presence of THCV. Future studies would benefit from taking these factors into consideration and from performing more frequent plasma sampling following THCV administration to elucidate its pharmacokinetics. Including the carboxylated metabolites of these cannabinoids (11-COOH-THC and 11-COOH-THCV) in the analysis would shed further light on this issue.

Pharmacological mechanisms

The pharmacological actions of THC have been well established and are mainly comprised of partial-agonism at the CB1 receptor. We have previously noted that THCV acts as a neutral antagonist in the lower dose range (Wargent et al., 2013), while acting as a weak agonist at higher doses (Hollister, 1974). The current study partly supports the notion of THCV as an antagonist, as impairments to delayed verbal recall and heart rate increase were successfully inhibited by THCV. However, the combination of both THC and THCV to significantly increase memory intrusions indicates a possible potentiating effect of THCV on specific domains of cognition.

Strengths and limitations

As the present study was a pilot study comprised of only ten volunteers, a larger study is needed to confirm the current findings. Due to the high variation in response to cannabinoids (Atakan, 2012; D'Souza et al., 2008; Englund et al., 2013; Morrison and Stone, 2011), it is likely that this study was underpowered to capture the variation in responses to THCV, with and without the presence for THC. Pharmacological interactions need to be explored using appropriate statistics, which this study was underpowered to do. Furthermore, the decision of timing and dosage of THCV were based on limited information, as pharmacokinetic data on THCV in humans are lacking. This may explain why so few plasma samples showed levels above quantification, although rapid redistribution of THCV still remains a possible explanation. Lastly, the aim of this study was to explore the potential protective effects of THCV on THC-induced psychotic and paranoid symptoms. This was prevented, as the lower dose of 1mg IV THC did not produce significant symptoms. Future studies should explore the effects of THCV using a higher dose of THC.

Controlled laboratory experiments using pure and isolated cannabinoids benefit from reducing inter-individual variation to explore specific psychopharmacological interactions. Intravenous administration of THC further reduces differences in bioavailability between subjects, as oral and inhaled administration suffers from poor bioavailability and high inter-individual variation (Grotenhermen, 2003). Furthermore, the within-subject design of the study particularly benefits cannabinoid studies, as it reduces variation between subjects, which otherwise would require a larger sample size. Although this study only recruited participants who had used cannabis 25 times or less to minimize variation between subjects, future studies would benefit from also recruiting frequent users, as they respond differently to cannabinoids (D'Souza et al., 2008).

Conclusion

In this small pilot study with healthy infrequent cannabis users, results indicate that the dose of 10mg oral THCV is well tolerated with no serious adverse reactions, and was subjectively not distinguishable from placebo. Furthermore, the lower dose of 1mg iv THC did not produce any significant short-term memory impairment, or psychotic or paranoid reactions. THCV significantly inhibited THC-induced impairment to delayed recall as well as THC-induced increase of heart rate. THCV on its own showed signs towards improved performance on the harder working-memory task, while also producing a slight increase in anxiety. However, these effects were small and need to be further studied in a larger sample.

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