Cannabis in the Arm: What Can we Learn from Intravenous Cannabinoid Studies?

Amir Englund[1],*, James M. Stone[2] and Paul D. Morrison[1]

[1]*King's College London, Institute of Psychiatry, Denmark Hill, London SE5 8AF;* [2]*Department College*

Abstract: Cannabis is widely used recreationally and for symptomatic relief in a number of ailments. However, cannabis has been implicated as a risk factor for the development of psychotic illness. For forty years researchers have utilised intravenous preparations of Δ^9-THC, as well as several other phytocannabinoids, in a laboratory setting. The intravenous route has the most reliable pharmacokinetics, reducing inter-individual variation in bioavailability and is well suited for the delivery of synthetic compounds containing a sole pharmacological moiety. Given the association between cannabinoids and psychotic illness, there has been a resurgence of interest in experimental studies of cannabinoids in humans, and the intravenous route has been employed. Here in a critical review, we appraise the major findings from recent intravenous cannabinoid studies in humans and trace the historical roots of this work back to the 1970's.

Keywords: Cannabis, Intravenous, delta-9-tetrahydrocannabinol, delta-9-tetrahydrocannabivarin, cannabidiol, THC.

INTRODUCTION

Cannabis is the world's most popular recreational drug, behind only alcohol and tobacco. The most recent figures estimate that between 125 - 203 million people around the world (4 million in the UK) used cannabis at least once in 2009 [1], and out of all first-time users around 10% become dependent [2]. Chronic cannabis use can be detrimental to memory and other cognitive functions [3], but these effects are largely reversible upon discontinuation of use [4].

Cannabis use has been associated with an increased risk of developing psychosis [5, 6], and worsening of symptoms for people with a pre-existing psychotic illness [7]. Patients who smoke cannabis have been found to relapse more frequently and have a poorer outcome [8]. Furthermore, with the growing popularity of strains of cannabis that have stronger psychoactive effects, such as "skunk" [9], the relevance of cannabis use to psychotic illness may be increasing. These stronger strains of cannabis have been hypothesised to carry a greater risk for psychosis [10] and to be more addictive [11].

Although the above findings are of concern, there are also beneficial effects of cannabis. Cannabis has been used for thousands of years as a treatment for various physical conditions as well as to 'improve' mood and appetite [12]. In medicine, cannabis preparations are used as anti-emetics for patients undergoing chemotherapy [13], appetite stimulants for people with HIV/AIDS, and to treat pain and spasticity in multiple sclerosis [14].

The cannabis plant is divided into three separate species, *Cannabis sativa*, *Cannabis indica*, and *Cannabis* [15]. The plant produces roughly 80 compounds referred to as phytocannabinoids [16, 17]. Among these cannabis compounds (cannabinoids), the most abundant, and largely responsible for the psychological effects of cannabis, is delta-9-tetrahydrocannabinol (Δ^9-THC) [18]. Other cannabinoids, some of which have very weak or no psychological effect, such as Δ^8-tetrahydrocannabinol (Δ^8-THC), Cannabidiol (CBD), Cannabigerol (CBG), Cannabinol (CBN), Cannabichromene (CBC), Cannabivarin (CBV), and Δ^9-tetrahydrocannabivarin (Δ^9-THCV), are believed to modulate the effect of Δ^9-THC depending on the concentration of the cannabinoid in the plant [18].

Cannabinoids exert their effect on the mind by interacting with the endocannabinoid system (ECS) [19]. The ECS refers to a set of endogenous ligands, their receptors, and the enzymes that synthesize and degrade them. Twenty years after the discovery of the structure of Δ^9-THC [20] researchers identified cannabinoid-specific receptors: cannabinoid receptor type-1 (CB$_1$R) [19], shortly followed by cannabinoid receptor type-2 (CB$_2$R) [21]. The cannabinoid receptors belong to the super-family of G-protein coupled receptors with densities about 10 to 50 times that of classical neurotransmitters, such as opioid or dopamine receptors [22]. The CB$_1$R is predominantly found in the central nervous system with the highest concentrations in the neocortex, basal ganglia, hippocampus, cerebellum, and anterior olfactory nucleus [23]. Moderate concentrations of CB$_1$R are also present in the hypothalamus, basolateral amygdala, and the periaqueductal gray matter in the midbrain. The CB$_2$R was initially thought to be localized only in immune cells in the periphery [24], but have more recently also been found in the cerebellum and brain stem [25].

To date, several endogenous cannabinoid receptor ligands have been found, although the most well known are arachidonoylethanolamide (Anandamide, AEA) [26] and 2-arachidonoylglycerol (2-AG) [27]. These are biosynthesized postsynaptically in an activity-dependant manner [28]. CB$_1$Rs are predominantly pre-synaptic, occurring at high density on the terminals of GABA-ergic neurons, and at lower density, on the terminals of glutamate-ergic terminals. Activation of CB$_1$Rs leads to a decrease of pre-synaptic neurotransmitter release. Endocannabinoids regulate GABA-ergic and glutametergic terminals over short and long-term durations by adjusting synaptic weights (Synaptic plasticity) [29]. Clearance of AEA and 2-AG is by a re-uptake mechanism and enzymatic hydrolysis, fatty acid amide hydrolase (FAAH) for AEA and monoacylglyceride lipase (MAGL) for 2-AG [30].

Endocannabinoid transmission is finely-tuned, with precise mechanisms for local synthesis and degradation. Administration of exogenous CB$_1$ agonists is unlikely to capture the subtleties of endocannabinoid signalling. Rather, disruption of endogenous cannabinoid dependent processes is more likely to occur. Also prolonged activation of CB$_1$Rs by Δ^9THC can lead to desensitisation and downregulation of the CB$_1$R. The effects of exogenous cannabinoids are critically dependent upon the dose. This has been demonstrated in rodents, where low doses of Δ^9THC exerted anxiolytic effects, while high doses produced anxiety [31]. Bidirectional effects have also been demonstrated in man [32]. These dose-dependent effects are also dependent on factors such as environment and previous exposure to the drug.

*Address correspondence to this author at the Psychosis Studies, The Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF, UK; Tel: +44(0)20 7848 1000; E-mail: amir.englund@kcl.ac.uk

ROUTE OF ADMINISTRATION

Cannabis is most commonly smoked as cigarettes or ingested orally. Naturalistic studies exploring the effects of recreational cannabis use on various outcomes benefit from allowing the participant to smoke or ingest the drug in a manner as similar to real life as possible [33]. One drawback however is that there are significant inter-individual differences in drug absorption from both oral and smoked routes of administration. For smoked cannabis, factors such as duration of smoking, puff duration, volume inhaled, smoking-skill, lung capacity, and loss of side-stream smoke may affect bloodstream cannabinoid concentrations [34, 35]. Orally consumed cannabinoids (either via capsules or food items) suffer from poor and irregular absorption [36], and are pharmacologically the least reliable. It is estimated that about 50% of the cannabinoids are lost due to stomach acids [37]. Intravenous (i.v.) administration on the other hand provides the most reliable delivery of synthetically prepared cannabinoids, with low inter-individual variability in drug plasma concentrations [38]. The plasma profile following an intravenous dose approximates that from the inhalational route [38]. Concentrations fall rapidly due to redistribution. Further reductions, attributable to drug metabolism, progress at a slower rate. Table **1** provides an overview of i.v. cannabinoid studies from the early 1970s to the present day.

INTRAVENOUS Δ^9-THC STUDIES

As Δ^9-THC is the main psychoactive component of cannabis, it is the molecule which has been most commonly used in i.v. studies.

Δ^9-THC is a partial agonist at the CB_1R and CB_2R with comparable affinity as the endocannabinoids anandamide and 2-AG, although with less efficacy [66]. The main psychological effects of cannabis use have been attributed to the activation of the CB_1R by Δ^9-THC [66, 67]. Work in the 1970s focussed on the pharmacokinetic and pharmacodynamic effects of i.v. administered Δ^9-THC [39, 40, 42, 43, 45]. In one of the first studies, Lemberger and colleagues [39] studied the clearance of a 0.5mg i.v. dose of Δ^9-THC. Hollister and colleagues [42] administered incremental doses (1-6mg) of i.v. Δ^9-THC to 4 healthy volunteers. After a return to baseline, each subsequent stepped dose was administered only to those participants who were able to tolerate the lower doses. The reported psychological effects on the participants were dose-dependent with increasing doses causing more intense experiences. Some of the milder symptoms were "feeling happy, dizzy, relaxed, visual perceptual changes, hunger, and sensitivity to sound"; while higher doses brought about "difficulty in concentration, poor memory, tension, flight of ideas, spontaneous laughter, and mental confusion". The authors concluded that 6mg approached the limit of tolerability.

The Yale THC Study Group, have carried out a series of studies using i.v. Δ^9-THC, making use of validated clinical assessment tools to measure psychological changes, and neurocognitive test batteries to follow changes in cognitive performance. They showed that i.v. administered Δ^9-THC can elicit transient schizophrenia-like positive psychotic symptoms and schizophrenia-like cognitive impairments in a proportion of healthy volunteers [54]. Δ^9-THC impaired cognitive performance in the domains of immediate and delayed recall, and in working memory [54]. Pre-treatment of healthy volunteers with Haloperidol (a dopamine D2 antagonist) did not protect against the psychotomimetic effects of Δ^9-THC and cognitive impairments were exacerbated [57]. The Yale group also studied the effects of i.v. Δ^9-THC in a sample of clinically stable schizophrenic patients. Δ^9-THC was shown to elicit transient psychotic symptoms and impair cognition [55], with no apparent benefits on mood.

Our group have used a similar approach in healthy volunteers and found that Δ^9-THC increased psychotic symptoms and cognitive impairments [59, 60, 61, 62, 63, 64, 65]. Participant-rated and investigator-rated positive symptoms were correlated and positive symptoms were not explained by anxiety [59]. Self-rated negative symptoms were also elicited by i.v Δ^9-THC [65]. In a subsequent study, we explored the co-administration of i.v. Δ^9-THC and CBD and found preliminary evidence that CBD protected against THC-elicited psychotic symptoms in 6 healthy volunteers [60]. We have also investigated the involvement of striatal dopamine release in Δ^9-THC induced psychotic symptoms using [123I]IBZM single photon emission tomography (SPET). We found that although Δ^9-THC increased positive psychotic symptoms, this was not accompanied by increased dopamine release as measured by single photon emission tomography (SPET) [61]. This is in agreement with a recent positron emission tomography (PET) study, where THC was administered orally [68].

In animal studies, CB_1 agonists impair neural oscillations, particularly in the theta (4-8Hz) and gamma ($\geq$40Hz) band [69,70, 71, 72]. We found that, in agreement with the animal work, the administration of 1.25mg i.v THC resulted in a reduction of theta power. In addition, coherence within the theta band between bi-frontal electrodes was significantly reduced. The latter EEG phenomenon was highly predictive of the degree of elicited positive psychotic symptoms [63]. Further analysis of this sample revealed yet another measure of neural synchrony, inter-trial-coherence (ITC), to be inversely correlated with measures of salience and identity disturbance [64].

Although there have been several fMRI studies using orally administered cannabinoids, there is to our knowledge, no fMRI work using the i.v. route.

OTHER CANNABINOIDS ADMINISTERED INTRAVENOUSLY

One of the first i.v. studies using cannabinoids other than Δ^9-THC gave three healthy male volunteers the hydroxylated metabolite of Δ^9-THC, 11-OH-Δ^9-THC [41]. This metabolite is also a CB_1 agonist, and it is said to be more potent than Δ^9-THC [48]. Two out of the three participants described the effects as very intense and were rated as unpleasant; although half an hour post-injection the "high" took on a more pleasurable quality. At the end of the study, the "high" had been described as being greater in intensity than they had previously experienced from cannabis.

In another study [43], participants were slowly infused with i.v. 11-OH-Δ^9-THC and told to ask for the termination of the drug as soon as they had reached the desired level of "high". The same procedure was used for Δ^9-THC which required a significantly higher dose to produce the same "high".

With the exception of Δ^9-THC, CBD is the cannabinoid that has been given intravenously most frequently. The receptor pharmacology of CBD has not yet been fully elucidated, but CBD has been shown to block some of the pharmacological effects of CB1 agonists [66]. CBD has been given i.v. in increasing doses to healthy participants. Neither 20mg [44], 30mg [45], nor 40mg [47] brought about any overt psychological changes in the participants tested, and no side effects were reported.

CBN is found to be a weak CB_1R partial agonist, with roughly 10% the potency of Δ^9-THC [66]. In one study [44], participants were slowly infused with increasing doses of CBN and were instructed to terminate the infusion when they reached the maximum tolerated "high". All participants who were given CBN tolerated it well and none asked to have the infusion stopped; they reported very mild and pleasant cannabis effects.

Δ^9-THCV is a CB_1R partial agonist which antagonises the receptor at low doses, but stimulates the receptor at higher doses[66]. The only study that explored i.v. Δ^9-THCV in healthy volunteers found it produced mild to moderate Δ^9-THC-effects for some, while others did not feel any change [48]. The authors concluded that 7mg of Δ^9-THCV was approximately 25% as potent as Δ^9-THC.

Table 1. **List of Intravenous Cannabinoid Studies with Cannabinoid Used, Dose, Duration of Infusion, and Outcome**

Year	Author	Participants	Cannabinoid given	Dose	Duration of infusion	Psychotic symptoms	Cognitive im-pairment	Observations
1970	Lemberger *et al.* [39]	3 healthy volunteers	Δ9-THC	0.5mg	Not reported	Not reported	Not reported	N/A
1972	Lemberger *et al.* [40]	12 long-term users	Δ9-THC	0.5mg	Not reported	Not reported	Not reported	N/A
1972	Lemberger *et al.* [41]	3 infrequent users	11-OH-Δ9-THC	1mg	Not reported	Not reported	Not reported	Participants reported greater "high" than they had experienced from smoking
1972	Hollister and Gillespie [42]	4 healthy volunteers	Δ9-THC	1-6mg	Not reported	Visual perception changes, mental confusion, "in-and-out" feeling.	Poor memory and difficulty concentrating (3mg and over)	Δ8-THC is slightly less potent than Δ9-THC
		3 healthy volunteers	Δ8-THC	1-9mg	Not reported	Similar to Δ9-THC	Similar to Δ9-THC	
1973	Perez-Reyes *et* . [43]	6 healthy volunteers	Δ9-THC	3.10±0.9mg	15-25 min	Not reported	Not reported	Δ9-THC produced a longer lasting and more intense 'high' than its metabolite
		6 healthy volunteers	11-OH-Δ9-THC	2.27±0.8mg	15-25 min	Not reported	Not reported	
1973	Perez-Reyes *et* . [44]	21 healthy volunteers	Δ9-THC	~ 4mg	15-25 min	Not reported	Not reported	Participants reported never have been so "high" from smoking cannabis after IV Δ9-THC
		6 healthy volunteers	CBN	~ 20mg	15-25 min	Not reported	Not reported	CBN produced a mild "high" at the higest dose.
		6 healthy volunteers	CBD	~ 20mg	15-25 min	Not reported	Not reported	CBD did not produce any psychological effect at any dose
1973	Hollister [45]	4 healthy volunteers	CBD	5-30mg	Not reported	Not reported	Not reported	CBD did not produce any psychological effect at any dose
1974	Perez-Reyes *et al.* [46]	30 frequent and infrequent users	Δ9-THC	53-68 µg/kg (3.71-4.76mg for 70kg)	15-25 min	Not reported	Not reported	N/A
1974	Perez-Reyes and Wingfield [47]	One epileptic patient	CBD	40mg	~ 16 min	Not reported	Not reported	N/A

Year	Author	Participants	Cannabinoid given	Dose	Duration of infusion	Psychotic symptoms	Cognitive impairment	Observations
1974	Hollister [48]	6 healthy volunteers	Δ9-THCV	7mg	Not reported	Not reported	Not reported	Mild to moderate side effects, similar to Δ9-THC reported
1977	Raft *et al.* [49]	10 healthy volunteers	Δ9-THC	0.022-0.044 mg/kg (1.54-3.08mg for 70kg)	Not reported	Increased anxiety	Not reported	N/A
1980	Hunt and Jones [50]	6 healthy volunteers	Δ9-THC	2mg	15 min	Not reported	Not reported	N/A
1980	Ohlsson *et al.* [38]	11 healthy volunteers	Δ9-THC	5mg	2 min	Not reported	Not reported	N/A
1981	Lindgren *et al.* [34]	18 light and heavy users	Δ9-THC	5mg	2 min	Not reported	Not reported	Light users were more intoxicated by IV Δ9-THC than heavy users
1983	Wall *et al.* [51]	12 healthy volunteers	Δ9-THC	2.2-4mg	15-25 min	Not reported	Not reported	N/A
1991	Volkow *et al.* [52]	8 occasional users	Δ9-THC	2mg	Not reported	Anxiety and paraoia in 2 participants	Not reported	3 out of 8 rated the experience as unpleasant
2004	Naef *et al.* [53]	8 cannabis naïve subjects	Δ9-THC	0.053mg/KG (3.71mg for 70kg)	2 min	Anxiety, hallucinations, perceptual change, strange ideas/mood	Not reported	No observed analgesic effect of Δ9-THC
2004	D'Souza *et al.* [54]	22 infrequent users	Δ9-THC	2.5 and 5mg	2 min	Paranoia, grandiose delusions, conceptual disorganisation, illusions, depersonalisation, slowing of time, blunted affect, emotional withdrawal, lack of spontaneity	Immediate, delayed recall and learning. Working memory for 'easy' task.	Verbal fluency and working memory for 'hard' task remained intact.
2005	D'Souza *et al.* [55]	13 stable (medicated) schizophrenic patients	Δ9-THC	2.5 and 5mg	2 min	Worsening in positive, negative, and general psychotic symptoms (PANSS). Increased perceptual alterations (CADSS).	Immediate/delayed recall, learning and vigilance	Worsening of anti-psychotic side effects
2008	D'Souza *et al.* [56]	30 frequent users	Δ9-THC	2.5 and 5mg	2 min	Perceptual alterations and psychotomimetic effects.	Immediate, delayed recall and learning.	Although Δ9-THC produced psychotic symptoms and cognitive impairments, this was significantly less compared to controls

(Table 1) Contd....

Year	Author	Participants	Cannabinoid given	Dose	Duration of infusion	Psychotic symptoms	Cognitive impairment	Observations
2008	D'Souza *et* . [57]	28 frequent and infrequent users	Δ9-THC (Haoperidol pretreatment)	0.0286mg/kg (2mg for 70kg)	20 min	Perceptual alterations and psychotomimetic effects.	Immediate, delayed recall and learning.	Pretreatment with Haloperidol worsened cognitive performance under Δ9-THC condition
2009	Zuurman *et* . [58]	21 infrequent users	Org 28611 (potent CB1 agonist)	0.3-10μg/kg (0.021-0.7mg for 70kg)	1 or 25 min (bolus or slow infusion)	Delusional perception, derealisation, confusional state, hallucinations	Attention	No adverse effects were experienced from bolus dose of 3μg/kg and less
2009	Morrison *et* . [59]	22 healthy volunteers	Δ9-THC	2.5mg	5 min	Positive symptoms (PANSS, CAPE), anxiety	Working memory, executive function	Psychotic symptoms were not related to levels of cognitive impairment or anxiety
2010	Bhattacharyya *et* . [60]	6 healthy volunteers	Δ9-THC, with CBD or placebo pretreatment	1.25mg (Δ9-THC) 5mg (CBD)	5 min 5 min	Positive symptoms (PANSS)	Not reported	Pretreatment with CBD protected against psychotomimetic effects of Δ9-THC
2010	Barkus *et* . [61]	10 healthy volunteers	Δ9-THC	2.5mg	5 min	Positive and general symptoms (PANSS)	Not reported	No significant dopamine release in the striatum following Δ9-THC
2010	Stone *et* . [62]	16 healthy volunteers	Δ9-THC	1.25mg	Not reported	Not reported	Subjective impairments to attention and concentration	Impaired time perception and estimation
2010	Morrison *et* . [63]	16 healthy volunteers	Δ9-THC	1.25mg	5 min	Positive, negative and general symptoms (PANSS)	Reduced accuracy on the hardest working memory task	Neural synchronicity (Theta-coherence) associated with psychotic symptoms
2011	Stone *et* . [64]	16 healthy volunteers	Δ9-THC	1.25mg	5 min	Paranoid ideations, anxiety, salience, identity disturbance, perceptual abnormalities	Not reported	Neural synchronicity (Inter-trial-coherence) associated with salience and identity disturbance
2011	Morrison *et* [65]	22 healthy volunteers	Δ9-THC	2.5mg	5 min	Negatice psychotic symptoms (PANSS, CAPE-state)	Not reported	Negative symptoms were not associated with sedation

Org 28611 is a synthetically derived, potent, CB_1R agonist [73]. Zuurman and colleagues [58] investigated Org 28611 for its potential sedative properties, and administered it i.v. to 21 infrequent cannabis users. They explored doses ranging from 0.3-10μg/kg (0,021-0,7mg for a 70kg individual) in either a slow 25 minute infusion, or a bolus infusion of 1 minute. Due to the adverse effects for the higher doses, 6-10μg/kg given as a slow infusion, these doses were not tested using bolus infusion. Participants reported symptoms such as delusional perception, derealisation, confusion, and hallucinations. The highest dose that was administered via bolus infusion was 3μg/kg (0,21mg for a 70kg individual), and was well tolerated by all participants.

DOSES AND PHARMACOKINETICS

Recreational cannabis use can be defined as self-titration of cannabis until desired level of intoxication has been reached. However, this level may easily be exceeded for reasons such as peer-pressure, alcohol use, and varying Δ^9-THC content of the cannabis used.

In one of the first i.v. Δ^9-THC studies [44], participants were given Δ^9-THC over 25min and asked to first mention when they felt when they had reached the desired level of "high" and then encouraged to receive the largest amount they could tolerate. The dose required for the desired level of "high" ranged between 11.26μg/kg to 26.28μg/kg (0.79mg to 1.84mg for a 70kg individual), while the maximum tolerated was between 36.98μg/kg to 69.3μg/kg (2.59mg to 4.85mg for a 70kg individual). After receiving the maximum tolerated dose, participants invariably reported never have been so "high" previously from cannabis. The more recent i.v. Δ^9-THC studies have used doses of 1.25mg, 2.5mg, and 5mg [54, 63]. These doses have been found to be psychotomimetic, anxiogenic, dysphoric and cognitively impairing. It may therefore be possible that doses which are considered by participants to be the strongest they have experienced reflect an over-intoxication, which in turn results in such symptoms.

Plasma concentrations of Δ^9-THC following i.v. administration are characterised by a steep increase in concentration followed by a rapid fall due to redistribution (Fig. **1**). Studies exploring the pharmacokinetics of different routes of administration have found i.v. and smoked routed to be very similar, both in terms of plasma concentrations as well as onset and offset of psychological effects [34, 38].

Table **2** provides a list of studies exploring plasma levels after inhaled and i.v. Δ^9-THC. The inhalation studies included in Table **2** were chosen as the amount of Δ^9-THC smoked was known, and participants either stopped when desired level of "high" was achieved [34, 38] or no increase in anxiety was reported [53, 74].

In a study by Lindgren and colleagues [34], heavy and light users were asked to smoke a cigarette containing 19mg Δ^9-THC and stop when they reached their desired level of "high". On a later occasion they were given an i.v. dose of 5mg Δ^9-THC. The following analysis of the plasma levels found Δ^9-THC concentrations to be approximately 67-98 ng/ml 3 minutes after smoking, and 288-302 ng/ml 3 minutes after i.v. injection. Subjective rating of "high" was significantly greater for the i.v. dose compared to when participants chose their own level of intoxication by smoking.

A more recent study gave participants half the above mentioned dose (2.5 mg) of i.v. Δ^9-THC. The participants had a mean (SD) plasma level of 68.0 (14.1) ng/ml 5 minutes after the injection; accompanied by psychotic symptoms, increased anxiety and dysphoria [59].

In contrast, Brenneisen and colleagues [74] asked participants to smoke a cannabis cigarette containing 70mg Δ^9-THC, 25mg of which was estimated to have been inhaled. Mean plasma (SD) Δ^9-THC 5 minutes post inhalation was 20.9 (16.9) ng/ml. No psychotic symptoms, anxiety or dysphoria were reported by the authors.
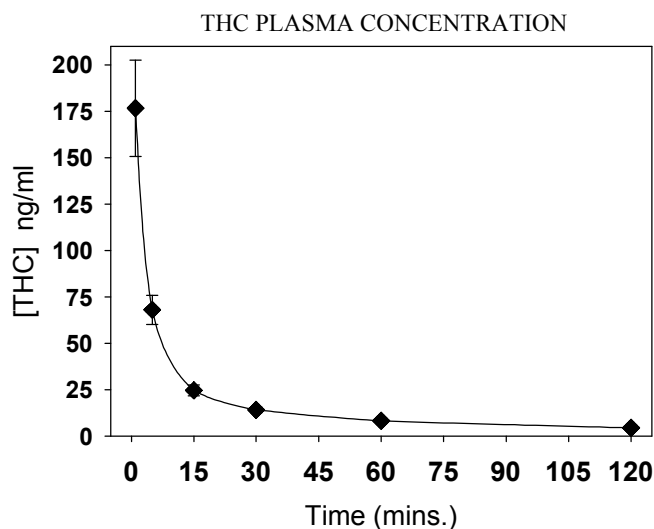

Fig. (1). Mean plasma concentrations following the intravenous administration of Δ^9-THC (2.5mg). Error bars show ± 95% CI [59].

Although results of plasma Δ^9-THC levels post administration are highly variable, due to factors such as drug preparation, time of sampling, type of assay used, etc., conclusions regarding the dose may still be drawn. In spite of some studies reporting plasma levels after i.v. Δ^9-THC being similar to inhaled Δ^9-THC, it is a relatively consistent finding that i.v. plasma levels are 2-3 times that of inhaled Δ^9-THC. This is especially true if participants self-titrate until they have reach their desired level of "high" [34, 38], or in studies where unpleasant reactions such as anxiety or dysphoria are not reported [74].

INDIVIDUAL DIFFERENCES

As expected, there is wide variation and individual reactions to i.v. Δ^9-THC. This is illustrated by i.v. studies administering high doses of Δ^9-THC to healthy volunteers, and observing psychotic symptoms, anxiety, and dysphoria. Volkow and colleagues [53] administered a 2mg i.v. dose of Δ^9-THC to 8 healthy volunteers, of whom two became anxious and one became paranoid.

In a study by Morrison and colleagues [60], 50% of their participants experience increased positive psychotic symptoms following a 2.5mg i.v. Δ^9-THC dose. D'Souza and colleagues [56] administered 2.5 mg and 5mg i.v. Δ^9-THC to both healthy volunteers and clinically stable schizophrenic patients. They observed 35% of the controls and 80% of patients displayed psychotic symptoms following 2.5 mg, while 50% of controls and 75% of patients did so after 5mg. Jointly, these observations suggest that about 35-50% of the psychiatrically healthy general population are susceptible to psychotomimetic effects and anxiety experienced from high doses of Δ^9-THC. Conversely, this means about half the general population are in some way resilient towards these effects. One possible hypothesis to this may be that these individuals have a naturally higher level of endocannabinoid activity.

CONCLUSION

There has been four decades of intravenous cannabinoid studies. Researchers have been able to investigate the actions of individual cannabinoid molecules, as opposed to smoked cannabis where the concentrations of a range of other components may be unknown. Intravenous administration also circumvents the problem of inter-individual variation in bioavailability. Most i.v. studies have focussed on Δ^9-THC. However there remains a need for more detailed information on i.v. Δ^9-THC dose-response relationships,

Table 2. List of studies reporting plasma Δ^9-THC levels using various routes of administration

Study	Route of administration		Dose	Mean plasma level ng/ml (SD) [Range]	Time of sample (post administration)
Ohlsson et al. [38]	i.v.		5mg	219 [161 - 316]	3 min
				62	10 min
	inhaled		13mg (range: 11.6-15.6)	77 [33 - 118]	3 min
Lindgren et al. [34]	inhaled				
		heavy users	12.7±1.3 mg	98 (44)	3 min
				64 (36)	6 min
		light users	13.4±1.6 mg	67 (38)	3 min
				46 (23)	6 min
	i.v.				
		heavy users	5mg	288 (119)	3 min
				128 (48)	6 min
		light users	5mg	302 (95)	3 min
				148 (42)	6 min
Volkow et al. [52]	i.v.		2mg	17 (12)	20 min
Naef et al. [53]	inhaled		0.053mg/kg	18.7 (7.4)	10 min
	i.v.		0.053mg/kg	271.5 (61.1)	5 min
Morrison et al. [59]	i.v.		2.5mg	68.0 (14.1)	5min
Barkus et al. [61]	i.v.		2.5mg	~60 (~5)	5 min
Brenneisen et al. [74]	inhaled		25mg	20.9 (16.9)	5min

especially for the lower dose range. There has also been a re-awakening of interest in other plant-derived cannabinoids, many of which were given by the i.v. route in the 1970s. In the intervening years it has become clear that the other cannabinoids also have a receptor pharmacology and central effects (albeit, more subtle than Δ^9-THC). Future work will hopefully shed light on the central properties of the other cannabinoids, as well as explaining individual differences to these compounds; taking advantage of the i.v. route.

CONFLICT OF INTEREST

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

REFERENCES

[1]   World Drug Report UNDOC. United Nations Office on Drugs and Crime [online]. http: //www.unodc.org/documents/data-and-analysis/WDR2011/World_Drug_Report_2011_ebook.pdf. Accessed on November 7th, 2011.
[2]   Hall W, Degenhardt L. Prevalence and correlates of cannabis use in developed and developing countries. Curr Opin Psychiatry 2007; 20(4): 393-7.
[3]   Pope HG, Jr., Gruber AJ, Hudson JI, Huestis MA, Yurgelun-Todd D. Neuropsychological performance in long-term cannabis users. Arch Gen Psychiatry 2001; 58(10): 909-15.
[4]   Grant I, Gonzalez R, Carey CL, Natarajan L, Wolfson T. Non-acute (residual) neurocognitive effects of cannabis use: a meta-analytic study. J Int Neuropsychol Soc 2003; 9(5): 679-89.
[5]   Arseneault L, Cannon M, Witton J, Murray RM. Causal association between cannabis and psychosis: examination of the evidence. Br J Psychiatry 2004; 184: 110-7.
[6]   Moore TH, Zammit S, Lingford-Hughes A, *et* . Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet 2007; 370(9584): 319-28.
[7]   Zammit S, Moore TH, Lingford-Hughes A, *et* . Effects of cannabis use on outcomes of psychotic disorders: systematic review. Br J Psychiatry 2008; 193(5): 357-63.
[8]   Caspari D. Cannabis and schizophrenia: results of a follow-up study. Eur Arch Psychiatry Clin Neurosci 1999; 249(1): 45-9.
[9]   Potter DJ, Clark P, Brown MB. Potency of delta 9-THC and other cannabinoids in cannabis in England in 2005: implications for psychoactivity and pharmacology. J Forensic Sci 2008; 53(1): 90-4.
[10]   Di Forti M, Morgan C, Dazzan P, *et* . High-potency cannabis and the risk of psychosis. Br J Psychiatry 2009; 195(6): 488-91.
[11]   Morgan CJ, Freeman TP, Schafer GL, Curran HV. Cannabidiol attenuates the appetitive effects of Delta 9-tetrahydrocannabinol in humans smoking their chosen cannabis. Neuropsychopharmacology 2010; 35(9): 1879-85.
[12]   Zias J, Stark H, Sellgman J, *et* . Early medical use of cannabis. Nature 1993; 363(6426): 215.
[13]   Meiri E, Jhangiani H, Vredenburgh JJ, *et* . Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. Curr Med Res Opin 2007; 23(3): 533-43.
[14]   Pertwee RG. Emerging strategies for exploiting cannabinoid receptor agonists as medicines. Br J Pharmacol 2009; 156(3): 397-411.
[15]   Hillig KW, Mahlberg PG. A chemotaxonomic analysis of cannabinoid variation in Cannabis (Cannabaceae). Am J Bot 2004; 91(6): 966-75.
[16]   Mechoulam R, Peters M, Murillo-Rodriguez E, Hanus LO. Cannabidiol--recent advances. Chem Biodivers 2007; 4(8): 1678-92.

[17]   Turner CE, Elsohly MA, Boeren EG. Constituents of Cannabis sativa L. XVII. A review of the natural constituents. J Nat Prod 1980; 43(2): 169-234.

[18]   Izzo AA, Borrelli F, Capasso R, Di M, V, Mechoulam R. Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. Trends Pharmacol Sci 2009; 30(10): 515-27.

[19]   Devane WA, Dysarz FA, III, Johnson MR, Melvin LS, Howlett AC. Determination and characterization of a cannabinoid receptor in rat brain. Mol Pharmacol 1988; 34(5): 605-13.

[20]   Mechoulam R, Gaoni Y. A total synthesis of DL-delta-1-tetrahydrocannabinol, the active constituent of hashish. J Am Chem Soc 1965; 87: 3273-5.

[21]   Munro S, Thomas KL, bu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. Nature 1993; 365(6441): 61-5.

[22]   Howlett AC, Bidaut-Russell M, Devane WA, Melvin LS, Johnson MR, Herkenham M. The cannabinoid receptor: biochemical, anatomical and behavioral characterization. Trends Neurosci 1990; 13(10): 420-3.

[23]   Glass M, Dragunow M, Faull RL. Cannabinoid receptors in the human brain: a detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. Neuroscience 1997; 77(2): 299-318.

[24]   Piomelli D. The molecular logic of endocannabinoid signalling. Nat Rev Neurosci 2003; 4(11): 873-84.

[25]   Suarez J, Bermudez-Silva FJ, Mackie K, *et* . Immunohistochemical description of the endogenous cannabinoid system in the rat cerebellum and functionally related nuclei. J Comp Neurol 2008; 509(4): 400-21.

[26]   Devane WA, Hanus L, Breuer A*et* . Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 1992; 258(5090): 1946-9.

[27]   Mechoulam R, Ben-Shabat S, Hanus L*et* . Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. Biochem Pharmacol 1995; 50(1): 83-90.

[28]   Cravatt BF, Giang DK, Mayfield SP, Boger DL, Lerner RA, Gilula NB. Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides. Nature 1996; 384(6604): 83-7.

[29]   Fernandez-Espejo E, Viveros MP, Nunez L, Ellenbroek BA, Rodriguez de FF. Role of cannabis and endocannabinoids in the genesis of schizophrenia. Psychopharmacology (Berl) 2009; 206(4): 531-49.

[30]   Dinh TP, Carpenter D, Leslie FM, Freund TF, Katona I, Sensi SL, *et* . Brain monoglyceride lipase participating in endocannabinoid inactivation. Proc Natl Acad Sci USA 2002; 99(16): 10819-24.

[31]   Viveros MP, Llorente R, Moreno E, Marco EM. Behavioural and neuroendocrine effects of cannabinoids in critical developmental periods. Behav Pharmacol 2005; 16(5-6): 353-62.

[32]   Phan KL, Angstadt M, Golden J, Onyewuenyi I, Popovska A, de WH. Cannabinoid modulation of amygdala reactivity to social signals of threat in humans. J Neurosci 2008; 28(10): 2313-9.

[33]   Morgan CJ, Schafer G, Freeman TP, Curran HV. Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: naturalistic study: naturalistic study [corrected] . Br J Psychiatry 2010; 197(4): 285-90.

[34]   Lindgren JE, Ohlsson A, Agurell S, Hollister L, Gillespie H. Clinical effects and plasma levels of delta 9-tetrahydrocannabinol (delta 9-THC) in heavy and light users of cannabis. Psychopharmacology (Berl) 1981; 74(3): 208-12.

[35]   Perez-Reyes M, Di GS, Davis KH, Schindler VH, Cook CE. Comparison of effects of marihuana cigarettes to three different potencies. Clin Pharmacol Ther 1982; 31(5): 617-24.

[36]   Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. Clin Pharmacokinet 2003; 42(4): 327-60.

[37]   Perez-Reyes M, Timmons MC, Lipton MA, Christensen HD, Davis KH, Wall ME. A comparison of the pharmacological activity of delta 9-tetrahydrocannabinol and its monohydroxylated metabolites in man. Experientia 1973; 29(8): 1009-10.

[38]   Ohlsson A, Lindgren JE, Wahlen A, Agurell S, Hollister LE, Gillespie HK. Plasma levels of delta 9-tetrahydrocannabinol after intravenous, oral, and smoke administration. NIDA Res Monogr 1981; 34: 250-6.

[39]   Lemberger L, Silberstein SD, Axelrod J, Kopin IJ. Marihuana: studies on the disposition and metabolism of delta-9-tetrahydrocannabinol in man. Science 1970; 170(964): 1320-2.

[40]   Lemberger L, Weiss JL, Watanabe AM, Galanter IM, Wyatt RJ, Cardon PV. Delta-9-tetrahydrocannabinol. Temporal correlation of the psychologic effects and blood levels after various routes of administration. N Engl J Med 1972; 286(13): 685-8.

[41]   Lemberger L, Crabtree RE, Rowe HM. 11-hydroxy- 9 -tetrahydrocannabinol: pharmacology, disposition, and metabolism of a major metabolite of marihuana in man. Science 1972; 177(43): 62-4.

[42]   Hollister LE, Gillespie HK. Delta-8- and delta-9-tetrahydrocannabinol comparison in man by oral and intravenous administration. Clin Pharmacol Ther 1973; 14(3): 353-7.

[43]   Perez-Reyes M, Timmons MC, Lipton MA, Davis KH, Wall ME. Intravenous injection in man of 9 -tetrahydrocannabinol and 11-OH- 9 -tetrahydrocannabinol. Science 1972; 177(49): 633-5.

[44]   Perez-Reyes M, Timmons MC, Davis KH, Wall EM. A comparison of the pharmacological activity in man of intravenously administered delta9-tetrahydrocannabinol, cannabinol, and cannabidiol. Experientia 1973; 29(11): 1368-9.

[45]   Hollister LE. Cannabidiol and cannabinol in man. Experientia 1973; 29(7): 825-6.

[46]   Perez-Reyes M, Timmons MC, Wall ME. Long-term use of marihuana and the development of tolerance or sensitivity to delta9 tetrahydrocannabinol. Arch Gen Psychiatry 1974; 31(1): 89-91.

[47]   Perez-Reyes M, Wingfield M. Letter: Cannabidiol and electroencephalographic epileptic activity. JAMA 1974; 230(12): 1635.

[48]   Hollister LE. Structure-activity relationships in man of cannabis constituents, and homologs and metabolites of delta9-tetrahydrocannabinol. Pharmacology 1974; 11(1): 3-11.

[49]   Raft D, Gregg J, Ghia J, Harris L. Effects of intravenous tetrahydrocannabinol on experimental and surgical pain. Psychological correlates of the analgesic response. Clin Pharmacol Ther 1977; 21(1): 26-33.

[50]   Hunt CA, Jones RT. Tolerance and disposition of tetrahydrocannabinol in man. J Pharmacol Exp Ther 1980; 215(1): 35-44.

[51]   Wall ME, Sadler BM, Brine D, Taylor H, Perez-Reyes M. Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women. Clin Pharmacol Ther 1983; 34(3): 352-63.

[52]   Volkow ND, Gillespie H, Mullani N, Tancredi L, Grant C, Ivanovic M, *et* . Cerebellar metabolic activation by delta-9-tetrahydrocannabinol in human brain: a study with positron emission tomography and 18F-2-fluoro-2-deoxyglucose. Psychiatry Res 1991; 40(1): 69-78.

[53]   Naef M, Russmann S, Petersen-Felix S, Brenneisen R. Development and pharmacokinetic characterization of pulmonal and intravenous delta-9-tetrahydrocannabinol (THC) in humans. J Pharm Sci 2004; 93(5): 1176-84.

[54]   D'Souza DC, Perry E, MacDougall L, *et* . The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. Neuropsychopharmacology 2004; 29(8): 1558-72.

[55]   D'Souza DC, bi-Saab WM, Madonick S, *et* . Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. Biol Psychiatry 2005 Mar 15; 57(6): 594-608.

[56]   D'Souza DC, Ranganathan M, Braley G, *et* . Blunted psychotomimetic and amnestic effects of delta-9-tetrahydrocannabinol in frequent users of cannabis. Neuropsychopharmacology 2008; 33(10): 2505-16.

[57]   D'Souza DC, Braley G, Blaise R, *et* . Effects of haloperidol on the behavioral, subjective, cognitive, motor, and neuroendocrine effects of Delta-9-tetrahydrocannabinol in humans. Psychopharmacology (Berl) 2008; 198(4): 587-603.

[58]   Zuurman L, Passier PC, de KM, Kleijn HJ, Cohen AF, van Gerven JM. Pharmacodynamic and pharmacokinetic effects of the intravenously administered CB1 receptor agonist Org 28611 in healthy male volunteers. J Psychopharmacol 2009; 23(6): 633-44.

[59]   Morrison PD, Zois V, McKeown DA, *et* . The acute effects of synthetic intravenous Delta9-tetrahydrocannabinol on psychosis, mood and cognitive functioning. Psychol Med 2009; 39(10): 1607-16.

[60]   Bhattacharyya S, Morrison PD, Fusar-Poli P, *et* . Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacology 2010; 35(3): 764-74.

[61] Barkus E, Morrison PD, Vuletic D, *et* . Does intravenous {triangleup}9-tetrahydrocannabinol increase dopamine release? A SPET study. J Psychopharmacol 2010 Sep 17.

[62] Stone JM, Morrison PD, Nottage J, Bhattacharyya S, Feilding A, McGuire PK. Delta-9-tetrahydrocannabinol disruption of time perception and of self-timed actions. Pharmacopsychiatry 2010; 43(6): 236-7.

[63] Morrison PD, Nottage J, Stone JM, *et* . Disruption of frontal theta coherence by Delta(9)-tetrahydrocannabinol is associated with positive psychotic symptoms. Neuropsychopharmacology 2011; 36(4): 827-36.

[64] Stone JM, Morrison PD, Brugger S, *et* . Communication breakdown: delta-9 tetrahydrocannabinol effects on pre-speech neural coherence. Mol Psychiatry 2011 Nov 1.

[65] Morrison PD, Stone JM. Synthetic delta-9-tetrahydrocannabinol clicits schizophrenia-like negative symptoms which are distinct from sedation. Hum. Psychopharmacol Clin Exp 2011; 26: 77-80.

[66] Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. Br J Pharmacol 2008; 153(2): 199-215.

[67] Mechoulam R, Shani A, Edery H, Grunfeld Y. Chemical basis of hashish activity. Science 1970; 169(945): 611-2.

[68] Stokes PR, Mehta MA, Curran HV, Breen G, Grasby PM. Can recreational doses of THC produce significant dopamine release in the human striatum? Neuroimage 2009; 48(1): 186-90.

[69] Robbe D, Montgomery SM, Thome A, Rueda-Orozco PE, McNaughton BL, Buzsaki G. Cannabinoids reveal importance of spike timing coordination in hippocampal function. Nat Neurosci 2006 Dec; 9(12): 1526-33.

[70] Hajos M, Hoffmann WE, Kocsis B. Activation of cannabinoid-1 receptors disrupts sensory gating and neuronal oscillation: relevance to schizophrenia. Biol Psychiatry 2008; 63(11): 1075-83.

[71] Hajos N, Katona I, Naiem SS, *et* . Cannabinoids inhibit hippocampal GABAergic transmission and network oscillations. Eur J Neurosci 2000; 12(9): 3239-49.

[72] Kucewicz MT, Tricklebank MD, Bogacz R, Jones MW. Dysfunctional prefrontal cortical network activity and interactions following cannabinoid receptor activation. J Neurosci 2011; 31(43): 15560-8.

[73] Morrison AJ, Adam JM, Baker JA, *et* . Design, synthesis, and structure-activity relationships of indole-3-heterocycles as agonists of the CB1 receptor. Bioorg Med Chem Lett 2011; 21(1): 506-9.

[74] Brenneisen R, Meyer P, Chtioui H, Saugy M, Kamber M. Plasma and urine profiles of Delta9-tetrahydrocannabinol and its metabolites 11-hydroxy-Delta9-tetrahydrocannabinol and 11-nor-9-carboxy-Delta9-tetrahydrocannabinol after cannabis smoking by male volunteers to estimate recent consumption by athletes. Anal Bioanal Chem 2010; 396(7): 2493-502.