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Actions of delta-9-tetrahydrocannabinol in cannabis:

Relation to use, abuse, dependence

ZIVA D. COOPER and **MARGARET HANEY**

Division on Substance Abuse, New York Psychiatric Institute and Department of Psychiatry, College of Physicians and Surgeons of Columbia University, New York, USA

Abstract

Cannabis use disorders have been recently identified as a relevant clinical issue: a subset of cannabis smokers seeks treatment for their cannabis use, yet few succeed in maintaining long-term abstinence. The rewarding and positive reinforcing effects of the primary psychoactive component of smoked cannabis, delta-9-tetrahydrocannabinol (THC) are mediated by the cannabinoid CB1 receptor. The CB1 receptor has also been shown to mediate cannabinoid dependence and expression of withdrawal upon cessation of drug administration, a phenomenon verified across species. This paper will review findings implicating the CB1 receptor in the behavioural effects of exogenous cannabinoids with a focus on cannabinoid dependence and reinforcement, factors that contribute to the maintenance of chronic cannabis smoking despite negative consequences. Opioidergic modulation of these effects is also discussed.

Prevalence of cannabis use and dependence

Delta (9)-tetrahydrocannabinol (THC), identified as the primary active component of cannabis (Felder & Glass, 1998), acts at the cannabinoid CB1 receptor to produce a wide-range of biological and behavioural responses. Many of these effects contribute to the abuse liability of cannabis, the most commonly used illicit drug worldwide (Bauman & Phongsavan, 1999). Recently, cannabis abuse and dependence has become recognized as a clinically relevant issue in the USA (Compton, Grant, Collier, Glantz, & Stinson, 2004). In 2002, it was reported that about 50% of 18 year olds reported using cannabis during their lifetime. Of these, 22.4% met DSM-IV criteria for cannabis abuse and 15.8% met DSM-IV criteria for cannabis dependence (Young et al., 2002). Approximately 90% of those who seek treatment for cannabis-related substance disorders report difficulty achieving and maintaining abstinence (Stephens et al., 2000). Some have attributed the increase in the prevalence of cannabis abuse and dependence to the increase in strength (THC concentration) of cannabis that is currently available (Compton et al., 2004). Although cannabis smokers titrate their cannabis exposure by smoking more of a low potency cannabis cigarette than high potency cigarette, the high potency cigarettes still result in significantly greater levels of plasma THC (Cooper & Haney, in press). Thus, the enhanced potency of cannabis exposes smokers to higher levels of THC, which may increase the chances of cannabinoid-induced behavioural and physiological dependence.

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Correspondence: Margaret Haney, PhD, New York State Psychiatric Institute, College of Physicians and Surgeons of Columbia University, 1051 Riverside Drive, Unit 120, New York, NY 10032, USA. Tel: (212) 543-6539. Fax: (212) 543-5991. E-mail: mh235@columbia.edu.

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It has been suggested that difficulty in achieving and maintaining abstinence may be partly due to a cannabis withdrawal syndrome, which includes symptoms such as irritability, anxiety, cannabis craving, and disrupted sleep. Approximately 61-96% of individuals experiencing withdrawal during abstinence use cannabis to alleviate the symptoms (Budney, Novy, & Hughes, 1999; Haney, 2005; Vandrey, Budney, Kamon, & Stanger, 2005), and 91% of adolescents in treatment for cannabis abuse report a persistent desire to smoke (Vandrey et al., 2005).

This review paper will focus on the neurobiological and behavioural effects mediated by the CB1 receptor that contribute to the abuse liability of cannabis. Animal studies have been useful in identifying CB1-mediated effects and clarifying variables that contribute to the induction of these effects. Studies investigating some of the variables, like route and schedule of administration (i.e. acute versus chronic), and CB1 agonist efficacy and potency, have provided the framework for human laboratory studies assessing behavioural effects of cannabis. Within the context of cannabis use and abuse, laboratory studies across species measuring the rewarding and reinforcing effects of cannabinoids model why cannabis is smoked on a periodic (recreational) and chronic basis. Reports of cross-species cannabinoid dependence and withdrawal provide an additional reference to explain the difficulty some chronic daily cannabis smokers have controlling their use. This paper will review the findings that implicate the CB1 receptor in cannabis's rewarding and reinforcing effects, and the development of cannabinoid dependence; factors, which likely contribute to the progression from periodic to chronic daily cannabis use.

Cannabinoids and reward

Similar to most drugs of abuse, THC and other CB1 agonists have been shown to activate the mesolimbic dopamine system (Tanda, Pontieri, & Di Chiara, 1997), the neurobiological substrate hypothesized to modulate the positive affective properties of a range of stimuli that reinforce behaviour in animals and humans. Conditioned place preference (CPP) is a behavioural assay that can be used to establish the rewarding effects of drugs in rodents by determining the positive affective quality of conditioned cues that have been paired with a drug. After several pairings of a test drug with a distinct drug-associated environment and saline in a distinct saline-paired context, the animal is placed between the two environments in a drug-free state and allowed to move between the drug- and saline-paired environments. Time spent in both environments is measured. More time spent in the drug-paired environment compared to the saline-paired environment indicates that the test drug produces positive conditioned effects. More time spent in the neutral environment (saline-paired context) compared to the drug-paired context indicates that the test drug elicits conditioned place aversion (CPA) (Bardo & Bevins, 2000).

As with most drug-induced effects, cannabinoids produce dose-dependent conditioned effects in this CPP assay. At high doses, both natural and synthetic cannabinoids produce CPA (Chaperon, Soubrie, Puech, & Thiebot, 1998; Cheer, Kendall, & Marsden, 2000; Hutcheson et al., 1998; McGregor, Issakidis, & Prior, 1996; Parker & Gillies, 1995). However, lower doses of CB1 agonists have been shown to produce CPP (Bairda, Iosue, Pegorini, & Sala, 2004; Bairda, Pozzi, Cavallini, & Sala, 2001; Bortolato et al., 2006; Lepore, Vorel, Lowinson, & Gardner, 1995; Valjent & Maldonado, 2000; Zarrindast, Nouri, & Ahmendi, 2007). This bidirectional effect of high versus low doses of cannabinoids is also reflected in reports of opposing drug effects in human cannabis smokers. Some report cannabis to produce good drug effects, increased relaxation, etc., while others report increased feelings of anxiety and paranoia (Reilly, Didcott, Swift, & Hall, 1998). In the CPP model, both the CPP observed at low doses and CPA produced by high doses of cannabinoids are blocked by the CB1 antagonist, SR141716A (Bairda et al., 2004; Chaperon et al., 1998). Taken together, these findings

demonstrate that the affective qualities of cannabinoids are dose-dependent, and the opposing conditioned effects (aversion versus preference) are directly mediated by the CB1 receptor. The neuroanatomical substrate that modulates the conditioned rewarding effects of cannabinoids has been recently identified in rats. Microinjections of THC specifically into the posterior ventral tegmental area (VTA) and posterior shell of the nucleus accumbens (NAS) produces CPP, an effect that is blocked by SR141716A (Zangen, Solinas, Ikemoto, Goldberg, & Wise, 2006).

Another procedure used to determine the rewarding effects of specific compounds is intracranial self-stimulation (ICSS). In the ICSS procedure, an animal is implanted with an electrode in the medial forebrain bundle of the mesolimbic pathway; the neuroanatomical site implicated in reward. Electrical stimulation to the medial forebrain bundle is reinforcing and thus maintains operant behaviour. An acute injection of a drug dose that decreases the baseline electrical stimulation that maintains operant behaviour (i.e. increases sensitivity to the electrical stimulation) suggests that the test drug dose is rewarding. A test drug dose that has aversive effects increases the threshold of electrical stimulation that is reinforcing (Wise, 1996).

Administration of THC and synthetic CB1 agonists including CP55-940, WIN-55,212-2 and HU-210 decrease the threshold for ICSS demonstrating the positive rewarding effects of cannabinoids in the rat. Administration of the CB1 antagonist SR141716A blocks CB1 agonist-induced effects on ICSS (Vlachou, Nomikos, & Panagis, 2005), indicating that the enhanced sensitivity of the brain-reward system by synthetic cannabinoids is directly due to CB1 activation. Interestingly, administration of the SR141716A alone increases the threshold for ICSS (Landsman, Burkey, Consroe, Roeske, & Yamamura, 1997), providing evidence for the role of endogenous cannabinoids in mediation of reward.

The drug discrimination (DD) procedure is used to assess the interoceptive effects of drugs in rodents, monkeys, and pigeons and establishes effects of a drug that may be related to its potential abuse (Ator & Griffiths, 2003). In DD procedures, an animal is trained to respond on a given manipulandum for food after administration of a training drug. A drug that shares similar discriminative effects as the training drug will produce responding on the manipulandum previously paired with the training drug, whereas a drug that does not share discriminative stimulus effects of the training drug will not elicit training-drug-appropriate responding. Anandamide, an endogenous ligand that binds to the CB1 receptor, shares discriminative stimulus effects with THC and other synthetic cannabinoids that act at the CB1 receptor (Solinas, Panlilio, Justinova, Yasar, & Goldberg, 2006; Solinas et al., 2007). The CB1 antagonist, SR141716A, blocks the discriminative stimulus effects of THC and synthetic cannabinoids in rats, demonstrating that these effects are mediated by the CB1 receptor (Jarbe, Lamb, Lin, & Makriyannis, 2001, 2006; Mansbach, Rovetti, Winston, & Lowe, 1996; Wiley, Lowe, Balster, & Martin, 1995; Wiley et al., 2004). THC discrimination has also been established in humans. Using the DD procedure, THC has been shown to share discriminative stimulus effects with the synthetic CB1 agonist, nabilone (Lile et al., 2008).

In human laboratory studies, robust increases in positive subjective ratings of intoxication such as 'good drug effect', 'high', and 'liking' are reported in volunteers after having smoked cannabis. These effects correspond to the concentration of THC in the cannabis, such that cannabis containing no THC (placebo) produces low to no subjective effects, and higher THC concentrations produce robust increases in ratings of subjective drug effects (Haney 2002; Haney, Comer, Ward, Foltin, & Fischman, 1997; Hart, van Gorp, Haney, Foltin, & Fischman, 2001; Hart, Ward, Haney, Comer, Foltin, & Fischman, 2002b; Haney, Ward, Comer, Foltin, & Fischman, 1999b, 2004; Kelly, Foltin, Emurian, & Fischman, 1997; Mendelson & Mello, 1984; Ward, Comer, Haney, Foltin, & Fischman, 1997; Zacny & Chait, 1991;). Oral THC also produces positive subjective effects and feelings of intoxication that are related to dose (Chait

& Zacny, 1992; Haney, 2007; Hart et al., 2002b; Hart Haney, Vosburg, Comer, & Foltin, 2005; Wachtel, ElSohly, Ross, Ambre, & de Wit, 2002). In regular cannabis smokers, oral THC (20 mg) and smoked cannabis (3.1% THC) produced similar subjective effects, with slightly higher ratings of 'high' and 'mellow' after the smoked cannabis compared to the oral THC and a longer time course of effects with oral THC compared with smoked cannabis (Hart et al., 2002b).

Positive subjective effects of smoked cannabis are blocked with daily treatment of the CB1 antagonist SR141716A (40 mg) for 8 days, although this blockade is not sustained after 15 days of antagonist administration (Huestis et al., 2007). An earlier study demonstrated that a single dose of 90 mg of the antagonist blocked the subjective effects of smoked cannabis (Huestis et al., 2001), but this finding was not replicated in the more recent study (Huestis et al., 2007). Interestingly, tolerance develops to the physiological (Benowitz & Jones, 1981) and subjective (Hart, Haney, Ward, Fischman, & Foltin, 2002a) effects of THC after repeated exposure to CB1 agonists (THC). Contrasting with the data demonstrating failure of the CB1 antagonist to block the subjective effects of cannabis when the antagonist is chronically administered, repeated administration of a CB1 agonist decreases subjective ratings of smoked cannabis. These findings provide some evidence that the subjective effects of cannabis are mediated through the CB1 receptor; however, further studies testing the effects of chronic administration and various doses of agonists and antagonists are needed.

Reinforcing effects of cannabinoids

The abuse liability of drugs can be predicted by their positive reinforcing effects in self-administration models of drug reinforcement, where access to drug is contingent upon some specified behavioural output. A drug serves as a positive reinforcer if the behaviour upon which its presentation is contingent increases or is maintained over time. Although cannabis abuse is prevalent among humans (see section on Prevalence below), the literature on animal self-administration of THC and synthetic cannabinoids is equivocal. Additionally, many of the studies that have demonstrated cannabinoid self-administration in rodents do so only under a limited set of conditions, such as food and water deprivation. Thus, cannabinoids do not seem to be as robust as other pharmacological reinforcers that maintain behaviour under a wide range of conditions (i.e., heroin, cocaine).

Evidence from animal literature that supports the positive reinforcing qualities of cannabinoids comes from findings that both mice and rats self-administer CB1 agonists in a dose-dependent manner (Deiana et al., 2007; Fadda et al., 2006; Fattore, Cossu, Martellotta & Fratta, 2001; Fattore et al., 2007; Martellotta, Cossu, Fattore, Gessa, & Fratta, 1998). Sensitivity to the positive reinforcing effects of cannabinoids has been shown to be sex-dependent in rats. Normal, cycling female rats acquire self-administration of the synthetic cannabinoid WIN55,212-2, at a faster rate and maintain higher rates of responding compared to male and ovariectomized female rats, indicating that ovarian hormones play a key role in modulating the reinforcing effects of cannabinoids in rats (Fattore et al., 2007). Others have demonstrated the reinforcing effects of cannabinoids to be directly regulated by the CB1 receptor by blocking cannabinoids self-administration with the CB1 antagonist, SR141716A (Fattore et al., 2001; Martellotta et al., 1998). The neuroanatomical substrate for the reinforcing effects of THC has been localized through a series of studies demonstrating behavior maintained by THC infusions directly into the posterior VTA and the shell of the NAS. Self-administration is antagonized by a systemic injection of SR141716A, again indicating that the reinforcing effects of localized infusions of cannabinoids are mediated by the CB1 receptor (Zangen et al., 2006).

The positive reinforcing effects of cannabinoids had been difficult to determine in non-human primates given that early studies failed to reliably demonstrate behaviour maintained by THC

and synthetic cannabinoids (Carney, Uwaydah, & Balster, 1977; Harris, Waters, & McLendon, 1974; Leite & Carlini, 1974; Mansbach, Nicholson, Martin, & Balster, 1994; Pickens, Thompson, & Muchow, 1973). Only recently has reliable dose-dependent self-administration of intravenous THC been reported in cocaine-experienced (Tanda, Munzar, & Goldberg, 2000) and drug-naïve monkeys (Justinova, Tanda, Redhi, & Goldberg, 2003). In light of previous negative findings, the self-administration supported by THC in the recent reports was attributed to the rapid rate at which THC was infused and the range of doses tested. Rate of infusion and broad dose ranges were variables that had not been manipulated in earlier studies. More recent studies using second-order schedules of reinforcement have demonstrated that THC-conditioned cues also maintain responding (Justinova et al., 2008). Similar to the findings in rodents, acute injections of SR141716A blocked THC self-administration and THC conditioned-cue responding, providing evidence that THC's direct and conditioned reinforcing effects are regulated by the CB1 receptor (Justinova et al., 2003, 2008; Tanda et al., 2000).

The reinforcing effects of cannabinoids are well documented in humans using laboratory self-administration procedures (Haney, 2008). These procedures are similar to animal self-administration paradigms in that the participant is required to emit a behavioural response on a manipulandum such as a joystick, computer mouse, or bicycle, or spend study earnings to gain access to a dose of drug. During a preliminary sampling session, the participant receives a dose of drug that will be later available for self-administration. The identity and dose of the sampled drug is not disclosed but is associated with some external cue including a letter, number, colour, etc. During the test session, the participant chooses to self-administer a previously sampled drug. Using these methods, cannabis is self-administered significantly more than placebo (0% THC) cannabis (Haney et al., 1997; Hart et al., 2001; Mendelson & Mello, 1984; Ward et al., 1997). Furthermore, cannabis with a higher THC concentration is preferred over cannabis with a lower THC concentration when participants are given a choice between the two strengths (Haney et al., 1997; Kelly et al., 1997; Ward et al., 1997). Similarly, oral THC is self-administered significantly more than placebo (Hart et al., 2005; Chait & Zacny, 1992). These studies provide evidence that THC is the primary component to the reinforcing effectiveness of cannabis in humans. No studies have yet tested the influence of CB1 antagonism on cannabinoid self-administration, so the precise role of the CB1 receptor in the reinforcing effects of THC in humans is not yet known.

Cannabinoid dependence and withdrawal

In animals and humans, repeated exposure to cannabinoids results in tolerance to CB1 agonist effects and physical dependence, defined by a withdrawal response that occurs upon cessation of drug administration (i.e., abstinence) (Jones, Benowitz, & Herning, 1981; Lichtman & Martin, 2005). Drawing from the animal and human literature, there are many lines of evidence implicating the CB1 receptor in the development of cannabis dependence and expression of withdrawal.

In rodents, pharmacologically-precipitated withdrawal using SR141716A has been extensively documented. Behaviours observed during precipitated withdrawal in rodents chronically administered cannabinoids include writhing, wet dog shakes, sniffing, front paw tremor, genital licking, erection, ataxia, ptosis, diarrhoea, mastication, decreased grooming, and piloerection (Tanda & Goldberg, 2003). SR141716A-precipitated withdrawal in mice is reversed with intravenous THC administration (Wilson, Varvel, Harloe, Martin, & Lichtman, 2006), and mice lacking the CB1 receptor fail to exhibit SR-141716A-induced THC withdrawal (Lichtman, Sheikh, Loh, & Martin, 2001). Being that withdrawal is precipitated by a CB1 antagonist and alleviated by THC, it is clear that cannabinoid dependence is largely mediated by the CB1 receptor in rodents.

Deprivation-induced THC withdrawal in non-human primates has been observed in monkeys treated with chronic intravenous THC for three weeks. Upon cessation of drug administration, increased aggressive behaviours (teeth baring and eye contact) were observed (Fredericks & Benowitz, 1980). The only early account of acquisition of THC self-administration in non-human primates was achieved during deprivation-induced THC withdrawal, pointing to the negative reinforcing effects of THC (Kaymakçalan, 1973). Robust drug discrimination of the CB1 antagonist, SR141716A was observed in monkeys chronically treated with THC (McMahon, 2006). When THC administration was terminated, SR141716A-appropriate responding was observed, indicating that the interoceptive cue of THC deprivation generalizes to the discriminative stimulus effects of SR141716A administered to chronically treated animals. When THC treatment was resumed, monkeys no longer exhibited SR141716A-appropriate responding (McMahon & France, 2003). Because termination of THC treatment produced a similar discriminative stimulus as SR141716A in monkeys chronically treated with THC (i.e. precipitated withdrawal), these data suggest that the interoceptive cues of cannabinoid deprivation-induced withdrawal is likely modulated by the CB1 receptor.

In humans, cannabinoid withdrawal was first described over 30 years ago following administration of oral THC (Jones, Benowitz, & Bachman, 1976, 1981) or smoked cannabis (Georgotas & Zeidenberg, 1979; Mendelson, Mello, Lex, & Bavli, 1984; Nowlan & Cohen 1977). Recent investigations have characterized the time course of the abstinence syndrome, the prevalence of symptoms, and variations in intensity of withdrawal as a function of the strength of smoked cannabis or dose of oral THC (Budney et al., 1999; Budney, Hughes, Moore, & Vandrey, 2004; Haney, Ward, Comer, Foltin, & Fischman, 1999a, 1999b; Haney et al., 2004; Kouri & Pope, 2000; Wiesbeck et al., 1996). Human laboratory studies have shown that termination of cannabis smoking or oral THC administration produces withdrawal symptoms including anger, irritability, anxiety, decreased appetite, weight loss, restlessness, disturbances in sleep onset and maintenance, and cannabis craving (Haney et al., 1999a, 1999b, 2004; Haney, Hart, Ward, & Foltin 2003; Hart et al., 2002a). Symptoms do not occur until about 24 hours after last use, peak in 2-3 days and last about 2-3 weeks (Budney et al., 2004). Similar to animal findings, cannabinoid withdrawal is alleviated by administration of smoked cannabis or oral THC (Budney et al., 2001; Budney, Vandrey, Hughes, Moore, & Bahrenburg, 2007; Haney et al., 1999a, 1999b, 2004; Hart et al, 2002a). This effect is dependent on cannabis strength and oral THC dose, again indicating that THC plays an essential role in the development of dependence and expression of withdrawal.

Opioidergic contribution to cannabinoid effects

In addition to CB1 receptor regulation of cannabinoids effects, there is substantial evidence indicating the contribution of the opioid system in cannabinoid reward, reinforcement, and dependence (see Robledo Berrendero, Ozaita, & Maldonado, 2008 for review). As described before, THC produces CPP and decreases the threshold for ICSS in rodents. These effects demonstrating cannabinoid-mediated reward are blocked by the mu-opioid receptor antagonist, naloxone (Braida et al., 2004; Gardner & Vorel, 1998). Additionally, the mu-opioid antagonist naltrexone shifted the dose-response curve for THC discrimination to the right, whereas the opioid agonist, heroin, shifted the curve to the left (Solinas & Goldberg, 2005). In both rodents and monkeys, opioidergic modulation of the reinforcing effects of THC and synthetic cannabinoids has been demonstrated. Opioid agonists facilitate reinstatement of the CB1 agonist, WIN-55,212-2, self-administration in rodents (Spano et al., 2004). Similarly, opioid antagonists diminish self-administration of the CB1 agonists, CP 55,940 (Braida et al., 2001), WIN-55,212-2 and HU 210 (Navarro et al., 2001) in rodents and THC self-administration in monkeys (Justinova, Tanda, Munzar, & Goldberg, 2004).

In parallel with the findings that opioidergic activity modulates the reinforcing and rewarding effects of THC, there is evidence of mu-opioid receptor modulation of THC dependence. Rodents chronically treated with THC exhibit opioid-like withdrawal syndrome when treated with the mu-opioid antagonist, naloxone (Hirschhorn & Rosecrans, 1974; Kaymakcalan, Ayhan, & Tulunay, 1977; Navarro et al., 1998, 2001). Coadministration of THC with naloxone prevents the development of cannabinoid dependence in rats (Tulunay, Ayhan, Portoghesi, & Takemori, 1981). In mice, the muopioid agonist, morphine, attenuates SR-141716A-induced THC withdrawal (Lichtman et al., 2001). Mice that lack the mu-opioid receptor (Lichtman et al., 2001), the opioid precursor, preproenkephalin (Valverde, Maldonado, Valjent, Zimmer, & Zimmer, 2000), or the delta opioid receptor (Castane, Robledo, Matifas, Kieffer, & Maldonado, 2003) demonstrate attenuated precipitated THC withdrawal. These findings indicate that the opioid system plays a role in development of cannabinoid dependence and expression of withdrawal in rodents.

The preclinical evidence of opioid modulation of cannabinoid effects has been difficult to demonstrate in humans. Although a low dose of naltrexone (12 mg) blunted the subjective effects of one dose of oral THC in cannabis smokers (20 mg; Haney et al., 2007), higher doses of naltrexone (50 mg) either had no effect (Wachtel & de Wit, 2000) or enhanced the subjective effects of oral THC (30 mg; Haney, Bisaga, & Foltin, 2003; Haney, 2007). Furthermore, contrary to data indicating that the opioid system modulates THC dependence in rodents, there is no evidence that naltrexone precipitates withdrawal in cannabis smokers (Haney et al., 2003; Haney, 2007). Thus, the precise opioid contribution to cannabis effects in humans remains to be clarified.

Conclusions

Across species, cannabinoids produce positive affective, rewarding, and reinforcing effects. Upon repeated drug administration, cannabinoid dependence develops marked by a withdrawal syndrome that is induced by either a cannabinoid antagonist or abstinence. The positive effects (reward and reinforcement) likely promote the occasional recreational use observed in cannabis abusers, whereas both the positive and negative effects of repeated use (i.e., cannabinoid dependence and withdrawal) contribute to the difficulty that a subset of cannabis smokers have achieving and maintaining abstinence. Across species the behavioural effects of cannabis, THC, and synthetic cannabinoids are clearly mediated by the endogenous cannabinoid system; the role of endogenous opioids in mediating cannabinoid effects in humans remain to be clarified.

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