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Cannabis reinforcement and dependence:

role of the cannabinoid CB1 receptor

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Abstract

Awareness of cannabis dependence as a clinically relevant issue has grown in recent years. Clinical and laboratory studies demonstrate that chronic marijuana smokers can experience withdrawal symptoms upon cessation of marijuana smoking and have difficulty abstaining from marijuana use. This paper will review data implicating the cannabinoid CB1 receptor in regulating the behavioral effects of Δ^9-tetrahydrocannobinol (THC), the primary psycho-active component of cannabis, across a range of species. The behavioral effects that will be discussed include those that directly contribute to the maintenance of chronic marijuana smoking, such as reward, subjective effects, and the positive and negative reinforcing effects of marijuana, THC and synthetic cannabinoids. The role of the CB1 receptor in the development of marijuana dependence and expression of withdrawal will also be discussed. Lastly, treatment options that may alleviate withdrawal symptoms and promote marijuana abstinence will be considered.

Keywords

cannabinoid; CB1; dependence; marijuana; THC; withdrawal

PREVALENCE OF MARIJUANA USE AND DEPENDENCE

Marijuana is the most commonly used illicit drug worldwide (UNODC 2007), and in the United States. Both marijuana potency and rates of marijuana abuse or dependence have been on the rise since the early 1990s (Compton *et al*. 2004). Among regular marijuana smokers, there is a subset who seek treatment for their marijuana use on their own initiative, and most (90%) of those who seek treatment do not succeed in remaining abstinent (Stephens, Roffman & Curtin 2000). One factor that likely contributes to these high rates of relapse is marijuana withdrawal, which includes symptoms such as irritability, anxiety, marijuana craving and disrupted sleep. Approximately 61-96% of individuals experiencing withdrawal during abstinence use marijuana to alleviate the symptoms (Budney, Novy & Hughes 1999; Haney 2005; Vandrey *et al*. 2005).

Daily marijuana use seems to be more prevalent among youths than the population at large. It is estimated that about 20% of American high school students who report having ever smoked marijuana become daily smokers (Johnston, O'Malley & Bachman 2001) and are therefore at risk for dependence, whereas it is estimated that 10% of the general public who ever used marijuana will become daily users (Johnston, O'Malley & Bachman 1995). In a community-

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based sample in the United States, 48.7% of 18-year-olds reported using marijuana at least once. Of those, 22.4% met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for cannabis abuse and 15.8% met DSM-IV criteria for cannabis dependence (Young *et al*. 2002). In Australia, 7% of young adults who participated in a longitudinal population study ($n = 1601$) met criteria for cannabis dependence. Adolescents in treatment for marijuana abuse also reported symptoms of marijuana withdrawal when abstaining from smoking (Vandrey *et al.* 2005), including a persistent desire to smoke (91%). Over one-third of those interviewed reported using marijuana to alleviate withdrawal (Coffey *et al*. 2002).

Evidence that daily marijuana smokers find it difficult to control their use of the drug, are distressed about the habit and experience withdrawal upon abstinence has led to a greater number of investigations on the behavioral and neurobiological effects of marijuana in an effort to understand how these effects may contribute to chronic marijuana use and consequent dependence upon the drug. Discovery of the cannabinoid receptors CB1 and CB2, as well as endogenous cannabinoids (anandamide) (for a review, see Felder & Glass 1998; Howlett *et al*. 2004), have also prompted interest in understanding the neurobiological effects of chronic marijuana use. This paper will review the findings that implicate the CB1 receptor in marijuana's rewarding and reinforcing effects, factors that likely contribute to the progression from periodic to chronic daily marijuana use. Additionally, the evidence that cannabis dependence exists, as characterized by the presence of withdrawal symptoms upon abstinence, and the role of the CB1 receptor in the development of dependence will be discussed.

REWARDING EFFECTS OF CANNABINOIDS AND THE CB1 RECEPTOR

Among the 60 different types of cannabinoids found in marijuana, Δ^9-tetrahydrocannabinol (THC) is the primary psychoactive component of the plant (Felder & Glass 1998). As with most drugs of abuse, Δ^9-THC activates the mesolimbic dopamine system (Ng Cheong Ton *et al*., 1988; French, Dillon & Wu, 1997; Tanda, Pontieri & Di Chiara 1997; Gardner 2005), the neurobiological substrate hypothesized to modulate the reinforcing and rewarding effects of a range of stimuli. In rodents, THC has been found to decrease the threshold for intracranial self-stimulation (ICSS), a procedure that is used to measure the reinforcing effects of electrical stimulation of the medial forebrain bundle, the neuroanatomical site implicated in reward (Gardner *et al*. 1988; Lepore *et al*. 1996). A stimulus that has rewarding effects (i.e. a drug with abuse liability) is predicted to decrease the threshold of electrical stimulation that is reinforcing, whereas a stimulus that has aversive effects is expected to increase the threshold of electrical stimulation that is reinforcing (Wise 1996). However, the evidence that high doses of synthetic CB1 agonists CP-55,940 and WIN-55,212-2 increase ICSS threshold, an effect that is blocked by the CB1 receptor antagonist SR141716A (Vlachou, Nomikos & Panagis 2005), demonstrates that the role of the CB1 receptor in this preparation is not entirely clear.

Another procedure used to assess the rewarding effects of a drug is conditioned place preference (CPP). This procedure measures the time spent in an environment that has been paired with a drug versus an environment that has not been paired with a drug. More time will be spent in the environment paired with a drug that induces positive conditioned effects compared with the neutral environment. In the case where the drug produces negative, aversive conditioned effects, it is expected that more time will be spent in the neutral environment than in the drug-paired environment (Bardo & Bevins 2000). Although high doses of natural and synthetic cannabinoids have been largely reported to produce conditioned place aversion (CPA) (Parker & Gillies 1995; McGregor, Issakidis & Prior 1996; Chaperon *et al*. 1998; Hutcheson *et al*. 1998; Cheer, Kendall & Marsden 2000), lower doses produce CPP (Lepore *et al*. 1995; Valjent & Maldonado 2000; Braida *et al*. 2001, 2004; Bortolato *et al*. 2006). Thus, CB1 agonists produce dose-dependent opposing behaviors: aversion at high doses and reward at low doses.

CB1 agonist-induced CPP and CPA are both blocked by administration of SR141716A (Chaperon *et al*. 1998; Braida *et al*. 2004), demonstrating that both effects are mediated by the CB1 receptor. The neuroanatomical substrate that modulates these rewarding effects of cannabinoids has been recently established in rats. Microinjections of THC into the posterior ventral tegmental area (VTA) and the posterior shell of the nucleus accumbens (NAS) produces CPP, an effect that is blocked by SR141716A (Zangen *et al*. 2006).

The drug discrimination procedure can also be employed to establish the effects of a drug that may be related to its potential abuse (Solinas *et al*. 2006). In drug discrimination procedures, animals are trained to respond on a given manipulandum after treatment with a particular drug. A compound of interest can then be assessed to determine if it shares similar discriminative stimuli (i.e. interoceptive cues) to the training drug. Anandamide, an endogenous ligand that binds to the CB1 receptor, increases dopamine release in the NAS and shares discriminative stimulus effects with THC and other synthetic cannabinoids that act at the CB1 receptor (Solinas *et al*. 2006, 2007). SR141716A blocks these discriminative stimulus effects in rats, demonstrating that the discriminative stimulus effects of cannabinoids are mediated by the CB1 receptor (Wiley *et al*. 1995, 2004; Mansbach *et al*. 1996; Järbe *et al*. 2001, Järbe, Liu & Makriyannis 2006).

In humans, robust increases in subjective effects such as ‘good drug effect’, ‘high’ and ‘liking’ are reported in volunteers after smoking marijuana. These effects correspond to the concentration of THC in the marijuana, such that marijuana containing no THC (placebo) produces few subjective effects, and higher THC concentrations produce greater increases in these subjective ratings (Mendelson & Mello 1984; Zacny & Chait 1991; Haney *et al*. 1997; 1999b; 2004; 2007; Kelly *et al*. 1997; Ward *et al*. 1997; Hart *et al*. 2001, 2002b; Haney 2002). Oral THC also produces positive subjective effects and feelings of intoxication that are related to dose (Chait & Zacny 1992; Hart *et al*. 2002b, 2005; Wachtel *et al*. 2002; Haney 2007). In fact, in regular marijuana smokers, oral THC (20 mg) and smoked marijuana (3.1% THC) produced similar peak subjective effects, with slightly higher ratings of ‘high’ and ‘mellow’ after the smoked marijuana compared with the oral THC, and a longer time course of effects with oral THC compared with smoked marijuana (Hart *et al*. 2002b). The subjective effects of smoked marijuana are blocked with daily treatment with the CB1 antagonist SR141716A (40 mg) for 8 days, an effect that dissipates after the 15th day of treatment (Huestis *et al*. 2007). An earlier study demonstrated that a single 90-mg dose of the antagonist blocked the subjective effects of smoked marijuana (Huestis *et al*. 2001), but this finding was not replicated in a later study (Huestis *et al*. 2007). These findings provide some evidence that the subjective effects of marijuana are mediated through the CB1 receptor. More research testing the effects of chronic administration and various doses of the antagonist is needed to elucidate the role of the CB1 receptor in the subjective effects of smoked marijuana.

REINFORCING EFFECTS OF CANNABINOIDS

Most drugs that are abused by humans demonstrate positive reinforcing effects in self-administration models in rodents and non-human primates. The literature on animal self-administration of THC and synthetic cannabinoids was, until recently, somewhat equivocal, with only a few studies reporting that self-administration of THC and synthetic cannabinoids is greater than vehicle self-administration. Studies that have shown that CB1 receptor agonists are self-administered in rodents report a blockade of this effect by pre-treatment with the CB1 antagonist SR141716A (Martellotta *et al*. 1998; Fattore *et al*. 2001). Furthermore, mice genetically lacking the CB1 receptor fail to self-administer the CB1 agonist WIN-55,212-2 (Ledent *et al*. 1999). Self-administration of THC directly into the posterior VTA and the shell of the NAS localizes the neuroanatomical substrate for the reinforcing effects of THC in rats. This effect is antagonized by a systemic injection of SR141716A, indicating that the reinforcing

effects are mediated by the CB1 receptor (Zangen *et al*. 2006). It is important to note that many studies reporting self-administration of CB1 agonists maintained the rodents on a restricted diet including food or water deprivation, demonstrating that the strength of such drugs as reinforcers is not as robust as other pharmacological stimuli (i.e. heroin, cocaine) that do not require food and water deprivation for acquisition and maintenance of the response.

Similar to rodent data, early studies in non-human primates failed to reliably demonstrate that THC and synthetic cannabinoids were reinforcing (Pickens, Thompson & Muchow 1973; Harris, Waters & McLendon 1974; Leite & Carlini 1974; Carney, Uwaydah, Balster, 1977; Van Ree, Slangen & de Wied 1978; Mansbach *et al*. 1994). THC did not support acquisition of self-administration even in non-human primates with an extensive history of self-administration of a variety of drugs (Pickens *et al*. 1973; Harris *et al*. 1974; Mansbach *et al*. 1994), a condition that usually facilitates acquisition of many pharmacological agents. 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 *et al*. 2003). The authors attribute these findings to the use of low doses and the rapid rate at which THC was infused, variables that were not manipulated in earlier reports. Self-administration of THC in both cases was blocked by SR141716A, providing compelling evidence that THC's reinforcing effects are regulated by the CB1 receptor (Tanda *et al*. 2000; Justinova *et al*. 2003).

In human laboratory studies, self-administration of smoked marijuana has been well established. Smoked active marijuana is self-administered significantly more than smoked placebo (0% THC) marijuana (Mendelson & Mello 1984; Haney *et al*. 1997; Ward *et al*. 1997; Hart *et al*. 2001), and marijuana with a higher THC concentration is preferred to marijuana with a lower THC concentration, additionally indicating that THC is the primary component to the reinforcing effectiveness of marijuana (Haney *et al*. 1997; Kelly *et al*. 1997; Ward *et al*. 1997). Similarly, oral THC is self-administered significantly more than placebo, demonstrating the positive reinforcing effects of oral THC (Chait & Zacny 1992; Hart *et al.* 2005). No studies have yet tested the influence of a CB1 antagonist on cannabinoid self-administration in humans, so the precise role of the CB1 receptor in the reinforcing effects of THC has not yet been demonstrated for this species.

MARIJUANA DEPENDENCE AND WITHDRAWAL

Physical dependence is defined by a withdrawal response that occurs upon cessation of drug administration (i.e. abstinence). Both pharmacologically precipitated and abstinence-induced withdrawal from cannabinoids have been observed in several species. There are many lines of evidence implicating the CB1 receptor in the development of marijuana dependence and expression of withdrawal.

Deprivation-induced withdrawal (abstinence) from chronic exposure to cannabinoids has yet to be studied in rodents. However, SR141716A-precipitated cannabinoid withdrawal has been extensively documented. Behaviors observed during precipitated withdrawal in rodents chronically administered cannabinoids include writhing, wet dog shakes, sniffing, front paw tremor, genital licking, erection, ataxia, ptosis, diarrhea, mastication, decreased grooming and piloerection (Aceto *et al*. 1995, 1996, 2001; Tsou, Patrick & Walker 1995; Rodríguez de Fonseca *et al*. 1997; Cook, Lowe & Martin 1998; Hutcheson *et al*. 1998; Tanda, Loddo & Di Chiara 1999; Costa, Giagnoni & Colleoni 2000; Lichtman *et al*. 2001a; Wilson *et al*. 2006; Touriño, Maldonado & Valverde 2007). SR141716A-precipitated withdrawal in mice exposed to marijuana smoke or intravenous THC is reversed with intravenous THC administration (Wilson *et al*. 2006), and mice lacking the CB1 receptor fail to exhibit SR141716A-induced THC withdrawal (Lichtman *et al*. 2001b). Because 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.

In non-human primates, consequences of withdrawal from THC have been observed (Fredericks & Benowitz 1980; Beardsley, Balster & Harris, 1986), but there are no published findings on the effects of antagonist-precipitated withdrawal. Thus, the reports on behavioral effects of withdrawal are strictly from deprivation-induced withdrawal. Monkeys treated non-contingently with a high dose of intravenous THC (0.4 mg/kg/injection) for 36 days demonstrated overt signs of withdrawal upon cessation of drug administration, such as anorexia, increased aggressiveness, tremors and yawning. These monkeys acquired THC self-administration in a state of dependence (Kaymakçalan 1973), the only early account of the reinforcing effects of intravenous THC in non-human primates. Additionally, disruption of schedule-controlled responding was observed in rhesus monkeys during THC abstinence, an effect that was reversed by THC administration (Beardsley *et al*. 1986). A quantitative study of behavioral tolerance to and dependence on chronic intravenous THC administration (2 mg/kg/day) for 3 weeks demonstrated significantly increased aggressive behaviors (teeth baring and eye contact) 1 week after cessation of drug administration (Fredericks & Benowitz 1980).

Non-human primates chronically treated with THC demonstrate robust discrimination of the CB1 antagonist SR141716A. Furthermore, upon termination of THC administration, SR141716A-appropriate responding is observed. When THC treatment is resumed, monkeys no longer exhibit SR141716A-appropriate responding. Because termination of THC treatment produces a similar discriminative stimulus to the CB1 antagonist SR141716A in monkeys chronically treated with THC, these data suggest that the interoceptive cues of cannabinoid deprivation-induced withdrawal is likely modulated by the CB1 receptor (McMahon & France 2003; McMahon 2006).

Precipitated withdrawal has not been tested in marijuana smokers due to limited availability of the drug for research in humans. The abstinence syndrome following administration of oral THC (Jones, Benowitz & Bachman 1976, Jones, Benowitz & Herning 1981) or smoked marijuana (Nowlan & Cohen 1977; Georgotas & Zeidenberg 1979; Mendelson *et al*. 1984) was described over 20 years ago. Since then, 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 marijuana or dose of oral THC (Wiesbeck *et al*. 1996; Budney *et al*. 1999, 2004; Haney *et al*. 1999a, 1999b; 2004; Kouri & Pope 2000). Abstinence from marijuana smoking and oral THC can produce symptoms such as anger, anxiety, decreased appetite, weight loss, irritability, restlessness and disturbances in sleep onset and maintenance (Haney *et al*. 1999a, 1999b, 2003; 2004; Hart *et al*. 2002a). These symptoms usually occur 24 hours after last use, peak in 2-3 days and last about 2-3 weeks (Budney *et al*. 2004) and is alleviated by administration of smoked active marijuana or oral THC (Jones *et al*. 1976; Haney *et al*. 1999a, 1999b; 2004; Budney *et al*. 2001, 2007; Hart *et al*. 2002a), indicating that THC plays an essential role in the development of dependence and expression of withdrawal.

TREATMENT FOR MARIJUANA DEPENDENCE

Compared with other drug dependencies (i.e. cocaine, heroin, alcohol), there are considerably fewer treatment programs available for marijuana dependence. This is likely due to the relatively recent awareness that marijuana relapse rates are as high as the relapse rates for other drugs of abuse. Withdrawal symptoms do not peak until several days after last marijuana use, so many daily smokers do not experience withdrawal because they are rarely abstinent for more than a 24-hour period. Additionally, it is likely that some users do not associate the withdrawal

syndrome with cessation of smoking because of the delayed onset of symptoms. Marijuana users experiencing withdrawal will often smoke marijuana in order to alleviate the symptoms (Stephens *et al*. 2000; Haney 2005), thus perpetuating chronic marijuana use.

Non-pharmacotherapies explored as treatment options for marijuana dependence include cognitive-behavioral therapy (CBT) (Stephens, Roffman & Simpson 1994; Copeland *et al*. 2001), which focuses on strategies for recognizing and coping with marijuana use; motivation enhancement therapy (MET) in combination with CBT; and contingency management in conjunction with MET and CBT. MET, a type of therapy that focuses on developing an individual's intrinsic motivation to change a particular behavior, combined with CBT demonstrates some therapeutic efficacy by reducing marijuana use (marijuana-free urine specimens) and improving retention rate in the treatment program. Contingency management further enhances the effectiveness of CBT and MET by decreasing marijuana use and increasing retention rate. Although these therapies seem promising in treating marijuana abuse, in the most successful of all therapies assessed (MET/CBT plus contingency management), only 46% of the participants completed the 8-week program and submitted at least one marijuana-free urine specimen. Furthermore, according to self-report data, 1-6 months after termination of treatment, participants smoked marijuana about 8 days per month (Carroll *et al*. 2006).

A range of medications have been tested in a human laboratory model of marijuana dependence, but no medication has yet been approved by the Food and Drug Administration to treat this disorder. The most promising medication to date is oral THC, which decreases marijuana craving and withdrawal symptoms including anxiety, insomnia, chills and loss of appetite at doses that do not produce intoxication (Haney *et al*. 2004). Divalproex, a mood stabilizer, also decreases marijuana craving but increases withdrawal-associated anxiety, irritability and lethargy (Haney *et al*. 2004), and did not show promise clinically (Levin *et al*. 2004). Interestingly, the antidepressant bupropion, an indirect noradrenergic and dopaminergic agonist (Ferris & Cooper 1993) that has therapeutic efficacy in treating nicotine withdrawal (Hurt *et al*. 1997), worsened the marijuana withdrawal syndrome, possibly due to its stimulating effects, which may have potentiated withdrawal symptoms such as anxiety and irritability (Haney *et al*. 2001). Nefazodone, a serotonin-2 receptor antagonist and a norepinephrine and serotonin reuptake inhibitor (Eison *et al*. 1990) used to treat depression and anxiety (Fawcett *et al*. 1995; Zajecka 1996), alleviated a subset of marijuana withdrawal symptoms, including anxiety and muscle pain (Haney *et al*. 2003). It is apparent from the existing literature that the therapeutic efficacy of a pharmacological treatment for marijuana dependence is contingent upon its ability to alleviate both the craving for marijuana and withdrawal symptoms (physical and mood disturbances) during abstinence. Such an agent would be expected to facilitate initiation and maintenance of abstinence and prevention of relapse.

CONCLUSIONS

A percentage of marijuana smokers progress from periodic, recreational use to a daily pattern of repeated use, which can produce dependence. The progression to and maintenance of this pattern of use reflects a variety of characteristics of the drug, including its profile of subjective effects, positive reinforcing effects and the ability of the drug itself to alleviate symptoms of cannabis withdrawal. Across species, the endogenous cannabinoid system, specifically the CB1 receptor, has been shown to mediate these behavioral effects of marijuana, THC and synthetic cannabinoids. Currently, the treatments investigated for chronic marijuana use and dependence have focused on a variety of behavioral and pharmacological therapies. However, treatment of marijuana dependence is in its infancy relative to treatments for dependencies on other abused drugs. Thus, further investigations of potential therapies that act directly or

indirectly on the endogenous cannabinoid system to alleviate the withdrawal syndrome, decrease the reinforcing effects of marijuana and prevent relapse are needed.

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