Review Article

FIGHTING DRUG DEPENDENCE BY BLOCKING CANNABINOID TYPE 1 RECEPTORS

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ABSTRACT

Drug dependence is a chronic relapsing brain disorder characterized by neurobiological changes that lead to a compulsion to take a drug with loss of control over drug intake. Abused drugs (cannabinoids, opioids, ethanol, nicotine and psychostimulants) by interacting with various neural pathways in brain induces pleasant state and responsible for relapses. All abused drugs have common property of elevating dopamine levels in nucleus accumbens. Currently the treatments available for drug dependence are not satisfactory and the most successful smoking cure clinic by using a combination of treatments achieve a success rate of less than 30%. Cannabinoid receptors are coexpressed in the brain reward circuitry and recent preclinical and human studies have suggested that ligands blocking the CB1 receptors offer a novel approach for patients suffering from drug dependence that may be efficacious across different classes of abused drugs. This review examines the role and current status of cannabinoid CB1 receptor antagonist in drug dependence.

KEY WORDS: Drug dependence, CB1 receptor, SR141716A.

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INTRODUCTION

Drug dependence is a chronic, relapsing disorder characterized by the compulsion for drug and taking precedence over other needs. It is widely recognized as serious health problem that is increasing in prevalence across the worldwide. Addictive substances, such as cannabinoids, opioids, ethanol, nicotine and psychostimulants (cocaine, amphetamine), induce pleasant states, which contribute to their recreational use. Common mechanism of addictive drugs is thought to increase of dopamine in brain reward pathways.[1] Although drug dependence involves many psychosocial, genetic and neuropharmacological mechanisms; drug treatment is one of the important components of the therapeutic approaches used for drug dependence. Currently the treatments available for drug dependence are not satisfactory. The most successful smoking cure clinics, using a combination of psychological and pharmacological treatments, achieve a success rate of less than 30% after one year of abstinence. It is obvious that additional resources will be needed to achieve control on drug dependence. Several therapeutic targets to reduce craving are under investigation. From this perspective, great discoveries of past decade were revelation of endocannabinoids and its role in reward pathway. The exact patho physiological phenomena of drug dependence remains elusive though many studies have shown that all commonly abused drugs act upon the brain reward circuitry to ultimately increase extracellular concentration of the neurotransmitter dopamine in the nucleus

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accumbens and other forebrain areas. Many drugs of abuse appear to increase dopamine levels by dramatically increasing the firing and bursting rates of dopamine neurons located in the nucleus accumbens.[1] There is evidence that 5-hydroxytryptamine (5-HT), glutamate and gamma-aminobutyric acid (GABA) also influence the mesolimbic dopamine pathway.[1] Also GABAergic neurons projecting from nucleus accumbens to ventral tegmental area has an inhibitory influence on dopaminergic neurons of nucleus accumbens.[2] Cannabinoid receptors are differentially co-localised with dopamine, serotonin and opioid receptors in the forebrain and interact to alter their levels.[3] Involvement of endogenous cannabinoid system in feeding, antinociception, short term memory regulation and movement control, immune and inflammatory responses has been documented.[4] Recently, endocannabinoids has been shown to have important role in reward pathway. Clinical evidence in human and behavioral studies in animals indicate that cannabinoid receptor antagonist, rimonabant, can reduce the self administration and craving for several commonly addiction drugs.[5] Cannabinoid and endocannabinoids act on 2 types of cannabinoid receptors (CB1 and CB2). CB1 receptors are predominantly present in the central nervous system (cerebellum, basal ganglia, limbic cortices, hippocampus, hypothalamus and different nuclei of extended amygdala). They are also present in peripheral tissues. On the other hand CB2 receptors are expressed mainly on immune cells.[6] Interestingly, an overlapping distribution of CB1 receptors with D_1, D_2, $5HT_3$, and $5HT_{1A}$ has been reported in several brain areas such as caudate putamen, olfactory tubercle, dentate gyrus, piriform and perirhinal cortex.[3] CB1 receptors are also co-localise with μ opioid receptors in brain area relevant for opioid withdrawal.[7] Mechanisms of interactions between CB1 with these receptors remain to be investigated. Interaction could take place at the level of intracellular signaling pathways, but recently heterodimerisation between different neurotransmitter receptors have also been reported. Thus arising the possibility that CB1 could also form heterodimers with this receptor.[8] CB1 and CB2 receptors are G protein coupled receptors. CB1 receptors couple through $G_{i/o}$ proteins, negatively to adenylate cyclase and positively to mitogen activated protein kinase. CB1 activation inhibits voltage gated L, N, and P/Q calcium channel or activating K^+ currents. CB1 receptor has mainly inhibitory action on neurons.[6]

BRAIN REWARD CIRCUITS AND CANNABINOID RECEPTOR

The central neuronal circuits known to be involved in mediating the rewarding aspects of most abused drugs originate with a subgroup of dopamine neurons located in an area of ventral tegmental area (VTA). These dopaminergic neurons target GABAergic neurons located in nucleus accumbens (NA) as well as neurons in frontal cortex.[9] VTA dopaminergic neurons are also inhibited by local circuit neurons.[10] NA sends reward relevant information to the ventral globus pallidus (GP). VTA, NA, GP are also interconnected via reciprocal collaterals that are critical for reward phenomena. In recent years, it has become clear that these brain reward nuclei also receive glutamergic inputs necessary for drug related reward behaviour.[11] Researchers have studied the ability of THC to increase dopaminergic function in the NA and its ability to alter dopaminergic neurons activity in the VTA.[12] Further studies demonstrated that THC and synthetic agonist of cannabinoid receptor WIN 55,212-2, HU 210, and CP 55940 increased neuronal firing rates in dopaminergic neurons in anesthetized and unanesthetized rats as well as in brain slices containing the VTA[13,14] These studies also reported that the effects of cannabinoid could be blocked with the CB1 receptor antagonist rimonabant. Cheer et al,[14] demonstrated cannabin increase the dopaminergic neuron firing directly as well as indirectly by affecting the local circuitry to increase dopaminergic neuron activity. This study also reported that $GABA_A$ receptor antagonist, bicuculline, blocked the effects produced by

HU 210. Studies examining the effects of cannabinoids on VTA dopaminergic neurons suggest that the activation of CB1 receptors within the VTA may account for some of the reward relevant aspects of cannabinoid exposure, additional sites within and external to reward pathway must also be considered. Clearly, more data are needed before firm conclusions regarding the effects of cannabinoid and their activation of dopaminergic neurons in the VTA can be reached.

In recent years, it has become apparent that many of the abused drugs affect the reward relevant brain areas with other than NA dopaminergic neurotransmission. Many of these drugs have been shown to inhibit GABA and glutamate neurotransmission in the NA.[1] Hoffman et al,[15] demonstrated that WIN 55,212-2 could reduce GABA release in the rat NA via CB1 receptors. Robbe et al,[16] reported glutamate release onto NA is also inhibited by cannabinoid agonist. They suggested that the reduction of glutamergic input to the NA by CB1 receptor activation would reduce the excitation of GABAergic NA neurons projecting to dopamine neurons in the VTA and thereby decreasing the inhibition of the dopaminergic neurons. Several recent studies have demonstrated that synaptic plasticity in brain reward circuits can be modified by commonly abused drugs.[17] Wilson et al,[18] demonstrated that endocannabinoid and CB1 receptors were required to observe the long term depression of glutamergic cortical synaptic input. This phenomenon is also present in NA. Further studies are needed to describe the significance of synaptic plasticity in reward relevant circuits and role in drug addiction. With further expansion in knowledge of the mechanisms of cannabinoid in the brain and precise description of action of endocannabinoids in the reward circuit more developments are underway in addictive process of drug.

Animal studies: A variety of animal models are used to study the cardinal feature of drug dependence. Drug discrimination, self administration, conditioned place preference; intracranial self stimulation and withdrawal state due to abrupt termination of action are commonly used animal models. Several interactions have been described between nicotine and cannabinoids in animals. Nicotine not only potentiates acute responses induced by THC but also at sub threshold dose of THC, which is unable to induce reward effects in CPP, it induces rewarding effects in this model. Also, nicotine enhances the effects of THC on c-FOS expression, which is a good index of neuronal activity, in various brain areas.[19] Studies have also shown that blockade of CB1 by rimonabant prevented the acquisition of nicotine induced CPP. Forget et al,[20] demonstrated rimonabant hampered the motivational value of nicotine in rats as well as short term capacity of nicotine paired conditioned stimuli. They suggested blockade of CB1 receptor can oppose tobacco dependence and withdrawal. In contrast, another study with CB1 knockout mice, nicotine was unable to produce positive place preference suggesting all actions of nicotine are not through CB1 receptor.[21] There is increased brain contents of endogenous ligand anandamide in the limbic forebrain on chronic exposure to alcohol and nicotine.[22] This increased endocannabinoid in reward system may be responsible for reinforcing properties of habit forming drugs. Interestingly SR141716 dose dependently blocked the dopamine releasing effects of nicotine in the nucleus accumbens and since dopamine release in nucleus accumbens is thought to play a major role in positive reinforcing effect of nicotine, this finding support a role for CB1 receptor in nicotine induced reward effects.[23] Specific interactions of the opioid and cannabinoid system are postulated which affects the reward related events. Evidence is available showing a functional cross talk between the cannabinoid and opioid systems in modulating the addiction behaviour. This interaction is bidirectional and involves release of opioid peptides by cannabinoids or release of endocannabinoids by opioids or involves interactions at the receptor level and/or their signal transduction mechanisms. In a study in mice opioid antagonist pretreatment reduced the self administration of

cannabinoid receptor agonist.[24] Further study showed development of a preference for a distinctive compartment associated with THC administration is lost in μ receptor knockout mice.[25]

Human studies: It were also undertaken to establish role of CB1 receptors in opioid induced reward. Mas-Nieto et al,[26] demonstrated CB1 antagonist, SR141716A, treatment induces withdrawal in chronically morphine treated mice similar to naloxone. CB1 receptor antagonist, SR141716A, has ability to abolish the rewarding effects of morphine by antagonizing the acquisition of morphine induced CPP. In another study opioid antagonist, naloxone was unable to induce withdrawal in morphine dependent CB1 knockout animals.[27] Reduction in the reinforcing effects of morphine was also observed in these knockout animals in intravenous self administration model. Recently, it has been reported that administration of the CB1 receptor antagonist SR 141716A can reduce heroin self administration in animals. Solinas et al,[28] demonstrated that blockade of CB1 receptor by SR141716 markedly reduced responding for intravenous heroin injection under an FR5 schedule of reinforcement and to a greater extent under a progressive ratio schedule of reinforcement in rats. Mascia et al,[29] demonstrated stimulation of dopamine release in mesolimbic system, in particular in the nucleus accumbens was absent upon morphine treatment in CB1 knockout mutants. Although the sites of action for ethanol's effect in the brain are poorly understood, ethanol's rewarding effects seems to be mediated through dopamine reward pathway. There is evidence also supporting the involvement of endocannabinoid system and CB1 receptor in some of the pharmacological and behavioural effects of ethanol. Increase in endogenous cannabinoid agonist anandamide has been found in response to chronic ethanol exposure in rodent model.[22] Chronic ethanol exposure has also been associated with downregulation of CB1 receptor number in rodents which may be due to overstimulation of receptors. CB1 receptor antagonist, rimonabant, reduced alcohol intake and craving in animals.[30] Houchi et al,[31] demonstrated CPP due to repetitive administration of ethanol was absent in CB1 knockout mice whereas cocaine induced place preference was not affected in knockout animals. In the same experiment they showed that there was absence of ethanol induced dopamine release in the nucleus accumbens in CB1 knockout mice. In another study disruption of CB1 receptor in mice resulted in decrease ethanol consumption and preference. Decrease ethanol self administration was also associated with increased sensitivity to acute intoxicating effects of ethanol.[32] All these findings suggest that CB1 receptor blockade may be an effective approach to the treatment in alcohol dependence in humans. Although less extensive investigations regarding the involvement of cannabinoid system in psychostimulant (cocaine and amphetamine) addiction has been done, evidence exists for interaction between cocaine and CB1 receptor. In this regard, Centonze et al,[33] demonstrated increased levels of the endocannabinoid anandamide in the striatum of rats in response to cocaine administration. Increased levels of anandamide were attributed to stimulation of its synthesis and inhibition of degradation. CB1 receptor antagonist blocked effect of cocaine on reward pathway. In another study synthetic cannabinoid agonist, HU210, administration was associated with relapse to cocaine after prolonged withdrawal in rats. Relapse associated by re-exposure was attenuated by selective CB1 receptor antagonist, SR141716A,[34] similarly the reward effects of methamphetamine in intravenous self administration model in rats was blocked by SR141716A.[35] In the same study attenuation of reinstatement inducing dose of methamphetamine was done by THC. Anggadiredja et al,[35] suggested that the endocannabinoid system, through arachidonic acid cascade, serves as a modulator of the reinstating effects of methamphetamine. Further experiments are needed to clarify the involvement of endogenous cannabinoid system in rewarding effects of psychostimulants.The development of animal model for THC has so far been unsuccessful.

Drug discrimination model is widely used for studying the cannabinoid effects in animals. SR141716A produces reversible, dose dependently antagonism effects of stimulant effect of THC.[36] This selective cannabinoid antagonist also precipitated withdrawal syndrome in cannabinoid dependent animals.[37] Recently, a squirrel monkey model of THC intravenous self administration has been developed. SR141716 entirely blocked the self administration of THC in squirrel monkeys.[38] In summary, these rodent models were instrumental in laying the initial groundwork pointing to further investigation into the effects of CB1 antagonism in humans. Most importantly, no significant toxic effects were associated with rimonabant administration in rodents.

Human studies: Role of CB1 antagonist, rimonabant, in drug dependence especially smoking cessation has been evaluated through human trials. Studies with rimonabant and tobacco use (STRATUS) program is prospective, randomized, multicenter, double blind, placebo controlled trials. This program enrolled more than 6,500 patients worldwide in three clinical trials (STRATUS-US, STRATUS-EU, STRATUS-WW) designed to explore the role of rimonabant in smoking cessation and long-term abstinence and prevention of weight gain upon smoking cessation.[39] STRATUS-US is a double-blind, placebo-controlled study, conducted in 11 sites in the United States. It enrolled 787 moderate to heavy smokers who smoked average 23 cigarettes a day. Patients received rimonabant (5mg or 20mg) or placebo for ten weeks.

Results of the study indicate that rimonabant 20mg doubled the odds of quitting vs. placebo (p=0.002). Among patients completing the study, prolonged abstinence was significantly higher in the patients treated with 20mg of rimonabant (36.2%) when compared with patients treated placebo (20.6%).[39] SRATUS-US also studied the effect of rimonabant on post cessation weight gain and metabolic syndrome and results are encouraging STRATUS- EU is one year. Phase-III clinical trial conducted throughout Europe at 32 clinical trial sites whereas STRATUS-WW is one year maintenance study conducted world wide in 54 sites.[39] Results of these trials are not available.

Current status of cannabinoid CB1 receptor antagonism in drug dependence: Despite advances in the understanding of neurobiological and behavioural mechanisms that lead to drug dependence effective treatment is still lacking. Moreover, treatments available for commonly abused drug are unsatisfactory and relapse rate is very high. Most of the patients relapse even after best treatment. Cannabinoid CB1 receptor antagonists represent a potential target for blocking the direct reinforcement effects of nicotine, ethanol and various other drugs of abuse. By reducing the motivational effects of drug, CB1 receptor antagonists might provide an effective means for preventing relapse to drug abusers. Currently the drug has been applied for FDA approval for drug dependence and the results are awaited.

CONCLUSION

Since our neurobiological understanding of the mechanisms of cannabinoid actions in the brain has increased dramatically in recent years, it is likely that more precise description of the actions of THC and of the endocannabinoids in these critical reward circuits will further improve our understanding of the addictive process in the future.

REFERENCES

1. Spanage lR, Weiss F. The dopamine hypothesis of reward: Past and current research. Trends Neurosci 1999;22:521-7.
2. Robbe D, Alonso G, Duchamp F, Bockaert J, Manzoni OJ. Localization and mechanisms of action of cannabinoid receptors at the glutamergic synapses of the mouse nucleus accumbens. J Neurosci 2001;2:109-16.
3. Hermann H. Marsicano G, Lutz B. Co expression of the cannabinoid receptor type 1 with dopamine and serotonin receptors in distinct neuronal subpopulations of the adult mouse forebrain. J Neurosci 2002;109:451-60.
4. Singh J, Budhiraja S. Therapeutic potential of cannabinoid receptor ligands: Current status. Methods Find Exp Clin Pharmacol 2006;28:177-83.
5. Maldonado R, Valverde O, Berrendero F. Involvement of the endocannabinoid system in drug addiction. Trends Neurosci 2006;29,225-32.
6. Pertwee RG. Pharmacology of cannabinoid CB_1 and CB_2 receptors. Pharmacol Thre 1997;74,129-80.

7. Navarro M, Chowen J, Rocio A, Carrera M, Del Arco I, Villanua MA, et al. CB_1 cannabinoid receptor antagonist induced opiate withdrawal in morphine dependent rats. Neuroreport 1998;9:3397-402.
8. Bouvier M. Oligomerization of G-protein-coupled transmitter receptors. Nat Rev Neurosci 2001;2:274-86.
9. Wise RA, Bozarth MA. Brain mechanisms of drug reward and euphoria. Psychiatr Med 1985;3:445-60.
10. Steffensen SC, Svingos AL, Pickel VM, Henriksen SJ. Electrophysiological characterization of GABAergic neurons in the ventral tegmental area. J Neurosci 1998;18:8003-15.
11. Carlezon WAJ, Wise RA. Microinjections of phencyclidine (PCP) and related drugs into nucleus accumbens shell potentiate medial forebrain bundle brain stimulation reward. Pshychopharmacology (Berl) 1996;128:413-20.
12. Chen JP, Paredes WLi J, Smith K, Lowinson J, Gardner EL. Delta 9-tetrahydrocannabinol produces naloxone-blockable enhancement of presynaptic basal dopamine efflux in nucleus accumbens of conscious, freely moving rats as measured by intracerebral microdialysis. Psychopharmacology (Berl) 1990;102:152-62.
13. Wu X, French ED. Effects of chronic delta9-tetrahydrocannabinol on rat midbrain dopamine neurons: An electrophysiological assessment. Neuropharmacology 2000;39:391-8.
14. Cheer JF, Marsden CA, Kendall DA, Mason R. Lack of response suppression follows repeated ventral tegmental cannabinoid administration: an in vitro electrophysiological study. Neuroscience 2000;99:661-7.
15. Hoffman AF, Lupica CR. Direct actions of cannabinoids on synaptic transmission in the nucleus accumbens: a comparison with opioids. J Neurophysiol 2001;85:72-83.
16. Robbe D, Alonso G, Duchamp F, Bockaert J, Manzoni OJ. Localization and mechanisms of action of cannabinoid receptors at the glutamatergic synapses of the mouse nucleus accumbens. J Neurosci 2001;21:109-16.
17. Saal D, Dong Y, Bonci A, Malenka RC. Drugs of abuse and stress trigger a common synaptic adaptation in dopamine neurons. Neuron 2003;37:577-82.
18. Wilson RI, Nicoll RA. Endogenous cannabinoids mediate retrograde signaling at hippocampus synapses. Nature 2001;410:588-92.
19. Valjent E, Mitchell JM, Besson MJ, Caboche J, Maldonado R. Behavioural and biochemical evidence for interactions between Ä9-tetrahydrocannabinol and nicotine. Br J Pharmacol 2002;135:564-78.
20. Forget B, Hamon M, Thiebot MH. Cannabin CB1 receptors are involved in motivational effects of nicotine in rats. Psychopharmacology (Berl) 2005;29,181:722-34.
21. Cossu G, Ledent C, Fattore L, Imperato A, Bohme GA, Parmentier M, et al. Cannabinoid CB1 receptor knockout mice fail to self administer morphine but not other drugs of abuse. Behav Brain Res 2001;118:61-5.
22. Gonzalez S, Cascio MG, Fernandez-Ruiz J, Fezza F, Di Marzo V, Ramos JA. Changes in endocannabinoid contents in the brain of rats chronically exposed to nicotine, ethanol or cocaine. Brain Res 2002;954:73-81.
23. Cohen C, Perrault G, Voltz C, Steinberg R, SoubrieP. SR 141716, a central cannabinoid (CB1) receptor antagonist, blocks the motivational and dopamine releasing effects of nicotine in rats. Behav Pharmacol 2002;13:451-63.
24. Goldberg SR, Munzar P, Justinova Z, Tanda G. Effects of naltrexone on intravenous self administration of ä-9-tetrahydrocannabinol (THC) by squirrel monkeys under fixed ratio and second order schedules, (abstracts) Symposium on the Cannabinoids, international cannabinoid research society, Burlington, 2001;102.
25. Ghozland S, Matthes HW, Simonin F, Filliol D, Kieffer BL, Maldonado R. Motivational effects of cannabinoids are mediated by ì-opioid and ê-opioid receptors. J Neurosci 2002;22:1146-54.
26. Mas-Nieto M, Pommier B, Tzavara ET, Caneparo A, Naseimento SD, Fur GL, et al. Reduction of opioid dependence by the CB_1 antagonist SR141716A in mice: evaluation of the interest in pharmacotherapy of opioid addiction. Br J Pharmacol 2001;132:1809-16.
27. Ledent C, Valverde O, Cossu G, Petitet F, Aubert JF, Beslot F, et al. Unresponsiveness to cannabinoids and reduced addictive effects of opiates in CB1 receptor knockout mice. Science 1999;283:401-4.
28. Solinas H, Panlilio LV, Antoniou K, Pappas LA, Goldberg SR. The cannabinoid CB1 antagonist N-Piperidinyl-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide (SR141716A) differentially alters the reinforcing effects of heroin under continuous reinforcement, fixed ratio, and progressive ratio schedules of drug self administration in rats. J Pharmacol Exp Ther 2003;306:93-102.
29. Mascia MS, Obinu MC, Ledent C, Parmentier M, Bohme GA, Imperato A, et al. Lack of morphine induced dopamine release in the nucleus accumbens of cannabinoid CB_1 receptor knockout mice. Eur J Pharmacol 1999;383:R1-R2.
30. Arnone M, Maruani J, Chaperon F, Theibot MH, Poncelet M, Soubrie P et al. Selective inhibition of sucrose and ethanol intake by SR141716, an antagonist of central cannabinoid (CB1) receptors. Psychopharmacology (Berl) 1997;132:104-6.
31. Houchi H, Babovic D, Pierrefiche O, Ledent C, Daoust M, Naassila M. CB_1 receptor knockout mice display reduced ethanol induced conditioned place preference and increased striatal dopamine D_2 receptors. Neuropsychopharmacology 2005;30:339-49.
32. Naassila M, Pierrefiche O, Ledent C, Daoust M. Decreased alcohol self administration and increased alcohol sensitivity and withdrawal in CB1 receptor knockout mice. Neuropharmacology 2004;46:24353.
33. Centonze D, Battista N, Rossi S, Mercuri NB, Finazzi-Agro A, Bernardi G, et al. A critical interaction between dopamine D2 receptors and endocannabinoids mediates the effects of cocaine on striatal gabaergic transmission. Neuropsychopharmacology 2004;29:1488-97.
34. De Vries TJ, Shaham Y, Homberg JR, Crombag H, Schuurman K, Dieben J, et al. A cannabinoid mechanism in relapse to cocaine seeking. Nat Med 2001;7:1151-4.
35. Anggadiredja K, Nakamichi M, Hiranita T, Tanaka H, Shoyama Y, Watanabe S, et al. Endocannabinoid system modulates relapse to methamphetamine seeking: possible mediation by the arachidonic acid cascade. Neuropsychopharmacology 2004;29:1470-8.
36. Wiley JL, Lowe JA, Balster RL, Martin BR. Antagonism of the discriminative stimulus effects of delta 9-tetrahydrocannabinol in rats and rhesus monkeys. J Pharmaco Exp Ther 1995;275:1-6.
37. Maldonado R, Rodriguez de Fonseca F. Cannabinoid addiction: behavioral models and neural correlates. J Neurosci 2002;22:3326-31.
38. Tanda G, Munzar P, Goldberg SR. Self administration behavior is maintained by active ingredient of marijuana in squirrel monkeys. Nat Neurosci 2000;3:1073-4.
39. Press release. http://en.sanofi-aventis.com/press/ppc_2698.asp#3 accessed June 23:2005.