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Neurobiological mechanisms of cannabinoid addiction

L. Fattore^{a,b}, P. Fadda^{b,c}, M.S. Spano^{b,c}, M. Pistis^{b,c}, W. Fratta^{a,b,c,*}

^a Institute of Neuroscience CNR, National Research Council, Section of Cagliari, Italy

^b Centre of Excellence “Neurobiology of Dependence”, Cagliari, Italy

^c Department of Neuroscience, University of Cagliari, Italy

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Abstract

The endocannabinoid system is implicated in the regulation of a variety of physiological processes, among which conditioning, motivation, habit forming, memory, learning, and cognition play pivotal roles in drug reinforcement and reward. In this article we will give a synopsis of last developments in research on cannabinoid actions on brain reward circuits coming from behavioral, neurochemical and electrophysiological studies. Central cannabinoid-induced effects as measured by animal models of addiction, *in vivo* cerebral microdialysis, *in vitro* and *in vivo* electrophysiological recording techniques, will be reviewed. Brain sites that have been implicated in the mediation of addictive cannabinoid properties include primarily the ventral tegmental area, the nucleus accumbens, and the medial prefrontal cortex, although the amygdala, the substantia nigra, the globus pallidus, and the hippocampus have also been shown to be critical structures mediating motivational and reinforcing effects of cannabinoids. Putative neurobiological mechanisms underlying these effects will be delineated.

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Keywords: Endocannabinoid system; CB1 receptor; Dependence; Reward; Abuse; Relapse

1. Introduction

Marijuana smoking is the world's third most popular form of illicit drug use after alcohol drinking and tobacco smoking, with 160 million people (equivalent to 4% of the world's adult population) using cannabis each year (UNODC, 2006). Marijuana produces clear pleasurable and wellbeing feelings which peak at around 20 min and are virtually vanished 3 h after its use (Ohlsson et al., 1980; Lindgren et al., 1981). Although cannabis dependence is moderate rather than severe, one in nine cannabis users satisfies the criteria for dependence, and the number of individuals requesting treatment for quitting cannabis use has been rising, particularly in Europe, Australia and United States (Murray et al., 2007).

Cannabis has been known as a medicine for several thousand years across many cultures. The discovery and cloning of the two subtypes of the G(i/o) protein-coupled cannabinoid receptors, the CB1-R and CB2-R, as well as the isolation

and characterization of different endogenous ligands, such as arachidonylethanolamide (anandamide, AEA) and 2-arachidonoylglycerol (2-AG), have opened new horizons in this field of research. Interest in the potential utility of cannabis-based medicines has been progressively increasing since observation of their beneficial effects in the treatment of chemotherapy-induced nausea and vomiting, appetite stimulation in patients with AIDS as well as in the relief from spasticity, neuropathic pain and sleep disturbances in patients with multiple sclerosis. Accordingly, a protective role of the endocannabinoid (eCB) system has been proposed by biochemical, genetic and pharmacological studies using models of epilepsy, stroke, head trauma and neurodegenerative disorders, such as Huntington's, Parkinson's and Alzheimer's diseases (reviewed in Bisogno and Di Marzo, 2007; Micale et al., 2007). Moreover, promising evidence indicates that manipulation of the eCB system could be of help in treating several mood and mental disorders such as anxiety and depression (Viveros et al., 2005; Mangieri and Piomelli, 2007; Serra and Fratta, 2007).

Besides the homeostatic control of emotions, the regulation of motivated behavior is among the most important functions in which the eCB system is engaged, especially for its impact on human diseases such food and drug addiction (Di Marzo and Matias, 2005; Fattore et al., 2004, 2007a). For example, it has

* Corresponding author at: Department of Neuroscience, Cittadella Universitaria di Monserrato, Monserrato-Cagliari 09042, Italy. Tel.: +39 070 6754313; fax: +39 070 6754312.

E-mail address: wfratta@unica.it (W. Fratta).

long been recognized that cannabinoid agonists stimulate food intake in animals, probably through enhancement of food palatability, while feeding-regulating hormones such as leptin can affect endocannabinoids synthesis in both the brain (Di Marzo et al., 2001) and periphery (Gómez et al., 2002). Further support of the role of the eCB system in regulating reinforcement processes activated by rewards of different nature stems from evidence that CB1-R blockade inhibits sucrose consumption (Arnone et al., 1997), while CB1-R activation increases food consumption elicited by electrical stimulation of the lateral hypothalamus, a brain area that participates in the regulation of food intake and incentive reward (Trojnar and Wise, 1991).

The distribution of cannabinoid receptors, both in the brain and in the periphery, along with the development of pharmacological tools to investigate their functions, has led to a substantial increase in efforts to develop cannabinoids as therapeutic agents. However, a major impediment to the development of therapeutic cannabinoid medications is the occurrence of untoward cognitive and euphoric side effects of these drugs. Therefore, unravelling the mechanisms through which these actions occur is essential to develop rational approaches to medication strategies.

The neuroanatomical substrates of brain reward typically involve neural loci and mechanisms associated with the medial forebrain bundle, located largely in the ventral limbic mid-brain. The mesolimbic dopamine (DA) system originating in the ventral tegmental area (VTA) is involved in neural mechanisms contributing to drug addiction and it is widely accepted that this system processes rewarding stimuli, such as food, sex, money and addicting drugs, i.e. stimuli that are positively reinforcing and can elicit positive hedonic reactions (Wise, 2004). Axons of VTA DA neurons project to forebrain areas such as the nucleus accumbens (NAc) and the prefrontal cortex (PFC). CB1-Rs are abundantly expressed in these brain areas as well as in other structures related to motivation and reward, such as the substantia nigra (SN) pars reticulata, the olfactory tubercle, the hippocampus and the amygdala, which strongly contribute to the motivational and addictive properties of cannabinoids. Recently, a general role for the eCB system in the control of conditioned drug-seeking has been proposed (see De Vries and Schoffelmeer, 2005, and references therein), as well as in the reinstatement of drug-induced reinstatement of extinguished drug-seeking behavior (see Fattore et al., 2007a,c, and references therein).

2. Cannabinoids and drug addiction

Numerous controlled laboratory studies indicated that marijuana serves as a positive reinforcer in humans (Mendelson and Mello, 1984; Foltin et al., 1989; Kelly et al., 1994b), and that delta9-tetrahydrocannabinol (THC) is an essential reinforcing component of marijuana (Kelly et al., 1994a; Haney et al., 1997). Content of THC, social context (i.e. work or social-access period) and presence of alternative reinforcers (i.e. snack food or money) may all significantly alter subjective-effect rating and marijuana intake in humans (Haney et al., 1997; Kelly et al., 1994a,b).

The abuse liability of cannabis derivatives has long been questioned, symptoms of abstinence in heavy marijuana users being quite rare to observe in humans (Hollister, 1986), probably because the slow clearance of cannabis from the body masks withdrawal symptoms. A first case of a withdrawal syndrome occurring in a woman after 21 days of marijuana smoking was reported by Mendelson et al. (1984), who described an abstinence syndrome beginning 10 h after cessation of marijuana smoking and lasting 96 h. Behavioral and physiological abstinence phenomena after frequent administration of doses as high as 210 mg/day of oral THC were also described (Haney et al., 1999). Over the past decade, demand for treatment for cannabis abuse has grown dramatically, and a large proportion of heavy users of hashish or ganja has difficulties in achieve and maintain drug abstinence (McRae et al., 2003). Although pioneering studies have recently started to individuate possible useful targets for the treatment of cannabis abuse in humans (Solinas et al., 2007a; Haney, 2007), marijuana dependence appears difficult to treat, and its use leads to a risk of relapse as high as those found for other drugs of abuse (Stephens et al., 1994; Spear et al., 1999; Moore and Budney, 2003).

At preclinical level, it has been now definitely established that cannabinoids act on the brain in a way similar to other drugs of abuse (Gardner, 2002), producing clear subjective effects and leading to drug-seeking and drug-taking behavior (Martellotta et al., 1998; Fattore et al., 2001, 2007b; Justinova et al., 2003, 2005; Spano et al., 2004; Fadda et al., 2006; Deiana et al., 2007). However, the eCB system is not only the primary site of action for the motivational and reinforcing properties of cannabinoids, but it also exerts an overall modulatory effect on brain reward pathways, thus participating in the addictive properties of most drugs of abuse, such as alcohol (Mechoulam and Parker, 2003), nicotine (Viveros et al., 2006; Forget et al., 2006), cocaine (Arnold, 2005), opioids (Navarro et al., 2001; Fattore et al., 2004, 2005a, 2007d; Spano et al., 2007), methamphetamine (MDMA) (Parrott, 2006), and salvinorin (Braidia et al., 2007a,b). Accordingly, mice not expressing the CB1-R do not self-administer morphine (Ledent et al., 1999; Cossu et al., 2001), are less sensitive to the motivational and reinforcing effects of nicotine (Cohen et al., 2005) and alcohol (Thanos et al., 2005), and do not show ethanol withdrawal symptoms (Racz et al., 2003).

Notably, high levels of CB1-Rs are present in the same brain regions, i.e. PFC, amygdala, NAc, and hippocampus, known to be involved in conditioned processes in laboratory animals and cue-elicited craving in human addicts (Everitt et al., 1999; Wang et al., 1999). In view of the evidence for an important role of CB1-Rs in the neuronal mechanisms underlying relapse to drug-seeking, blockade of the CB1-R is particularly effective in reducing drug- and cue-induced reinstatement of drug-seeking behavior in abstinent animals (Fattore et al., 2003, 2005b; Spano et al., 2004; De Vries et al., 2005; Filip et al., 2006; Xi et al., 2006; Economidou et al., 2007), as well as in preventing relapse in human cigarettes smokers (Le Foll and Goldberg, 2005).

As a result of a magnitude of behavioral, neurochemical and electrophysiological studies, the past years have witnessed a thoroughly remarkable advance in the elucidation of the neu-

robiological mechanisms underlying the reinforcing properties of cannabinoids and their actions on brain's reward system.

2.1. Behavioural evidence

Human addictive behavior can be successfully modeled in laboratory animals, with seemingly good face validity to the human situation. In this paragraph, evidence for the motivational, discriminative, conditioning and positive reinforcing effects of cannabinoids as revealed by animal models of addiction are reviewed.

It has been long recognized that laboratory animals, from rodents to monkeys, repeatedly self-administer through lever-pressing activity a mild electrical stimulation of specific brain sites, which has been found to be extremely pleasurable in humans. The first behavioral evidence that cannabinoids possess addictive potential was given by Gardner's group which demonstrated that low doses of THC are able to lower brain reward threshold, i.e. to enhance electrical brain stimulation reward (BSR) (Gardner et al., 1988; Gardner and Lowinson, 1991). In line with this, withdrawal from a single administration of THC is able to elevate the threshold for BSR (Gardner and Vorel, 1998). More recently, the synthetic CB1-R agonists WIN 55,212-2 and CP 55,940 have also shown to increase the threshold for BSR (Vlachou et al., 2005), although lack of effects of CP 55,940 was reported by one study using similar experimental conditions (Arnold et al., 2001). Subsequent observation by Gardner et al. of the existence of strain differences in such a behavior (Lepore et al., 1996) deserves special mention, as it represents the first demonstration of the key role played by this feature (i.e. animal strain) in rendering the addictive properties of cannabinoids manifest in behavioral protocols (see also below). Intriguingly, behavioral findings by Lepore et al. (1996) closely parallel the neurochemical ones reported by the same group, with THC producing robust enhancement of both BSR and accumbal DA level in drug-preferring Lewis rats, a moderate BSR and accumbal DA level enhancement in drug-neutral Sprague–Dawley rats, and no effect in drug-resistant Fisher 344 strain (Chen et al., 1991; Gardner, 2002).

Based on the assumption that the same components of a drug's action subserve discriminative stimulus (DS) effects in animals and subjective effects in humans, drug discrimination (DD) techniques are used to study abuse-related effects by establishing the interoceptive properties of a training drug as a cue for performing a specific operant response (Solinas et al., 2006). DD procedures typically involve training an animal to produce a particular response (lever-press or nose-poke) in a given drug state for a food reinforcer and to produce a different response in the placebo or drug-free state. The interoceptive cue state (produced by the drug) controls the behavior as a DS or cue that informs the animal to make the appropriate response in order to gain reinforcement. The choice of response that follows administration of an unknown test compound can provide valuable information about the similarity of that drug's interoceptive properties to those of the training drug.

Studies employing this model have demonstrated that activation of CB1-Rs induces interoceptive effects in gerbils (Järbe

et al., 1975), pigeons (Henriksson et al., 1975), rodents (Balster and Prescott, 1992), and monkeys (Wiley et al., 1995). Cannabinoid DS effects show high pharmacological specificity, as they are selectively blocked by CB1-R antagonists, although a partial overlap has been reported with diazepam (Mokler et al., 1986; Wiley and Martin, 1999), phencyclidine (Doty et al., 1994), and pentobarbital (Alici and Appel, 2004).

Cannabinoid behavioral effects have been extensively investigated also by conditioned place preference/aversion testing, a behavioral method believed capable of measuring the affective (positive, neutral or negative) properties of psychoactive drugs. The conditioned place preference (CPP) procedure is typically used to infer incentive motivational values of addictive drugs, and is based on the ability of a neutral stimulus to acquire incentive salience (Tzschentke, 1998, 2007). Basically, animals experience two distinct neutral environments that during a conditioning period are spatially and temporally paired one with the training drug (drug-paired environment) and the other one with saline (non-drug-paired environment). At the end of the conditioning, the animal is given the opportunity to choose to enter and explore both environments, and the time spent in each environment is measured. The animal's choice to stay longer in the drug-paired environment is assumed to be an expression of the positive reinforcing experience within that environment, and is therefore considered an index of the reinforcing value of the drug.

Depending on a number of experimental parameters (CB1-R agonist dose and/or potency, strain of animals) and procedural features (number of conditioning sessions, previous priming drug injections), cannabinoids have been reported to induce both conditioned place preference and aversion, or showed neither statistically significant preference or aversion. Interestingly, the endocannabinoid transport inhibitor AM404 induces CPP in rats housed under enriched conditions, but not in rats kept in standard cages (Bortolato et al., 2006). Altogether, these studies have revealed a dose-dependent switch from reward to aversion, with low and high doses of cannabinoids inducing reward and aversion, respectively. An analogous phenomenon has been observed in human addicts, where low doses of THC or levonantradol are perceived as rewarding while higher doses as aversive (Noyes et al., 1975, Raft et al., 1977; Laszlo et al., 1981).

Drug self-administration (SA) paradigms are used for assessing drug-taking behavior, which can be investigated acutely in drug-naive animals, or chronically in animals trained to self-administer the drug. In these protocols, animals are allowed to self-administer a drug by pressing a specific lever or by inserting the nose into a specific hole provided with a photo beam. A correct lever-pressing or nose-poking response will result in the contingent presentation of reward, i.e. an intravenous infusion of the drug delivered by a computer-controlled syringe pump. At present, chronic SA procedures represent the most reliable animal model of addiction, which most closely resembles the human situation, allowing studying addictive behavior during all its phases, from initial acquisition of drug-taking behavior to extinction of such a behavior in absence of the drug, up to the reinstatement of drug-seeking following exposure to a drug or cue priming. Importantly, under controlled experimen-

tal conditions, laboratory animals do self-administer almost all drugs abused by humans, and in absence of physical dependence (Bozarth and Wise, 1984; Gardner, 1997, 2000).

Despite earlier reports of failure, more recent studies showed persistent and dose-dependent cannabinoid SA under different experimental conditions. Thus, intravenous SA of THC and AEA has been demonstrated in squirrel monkeys (Justinova et al., 2003, 2005), intravenous SA of WIN 55,212-2 has been reported in drug-naive mice (Martellotta et al., 1998; Fratta et al., 1999; Ledent et al., 1999; Fattore et al., 2002) and trained rats (Fattore et al., 2001, 2007b; Spano et al., 2004; Fadda et al., 2006; Deiana et al., 2007), while intracerebroventricular SA of CP 55,940 has been described in rats (Braidia et al., 2001). Interestingly, cannabinoid SA is observed at very low doses, and is promptly blocked by pretreatment with CB1-R antagonists. Recently, a study from our laboratory has confirmed that, in line with the cannabinoid-induced enhancement of mesolimbic DA release and BSR threshold (Chen et al., 1991; Lepore et al., 1996), intravenous cannabinoid SA in rats also depends on the specific strain of animal used, such a behavior being clearly evident in Lister Hooded and Long Evans, but not Sprague–Dawley rats (Deiana et al., 2007). Moreover, cannabinoid intake by trained rats is significantly affected either by sex, females acquiring stable cannabinoid intake at higher rates and more rapidly than males, and by ovarian function, ovariectomised females being less sensible to cannabinoid rewarding effects than intact counterparts (Fattore et al., 2007b). Notably, the existence of sex differences in drug self-administration is an additional trait that cannabinoids share with other drugs of abuse (Fattore et al., 2008).

Consistent with these preclinical observations, the influence of non-pharmacological variables (i.e. environmental setting, previous experience with the drug, personal expectation) on the subjective effects of marijuana in humans is known since early clinical studies (Hochman and Brill, 1971; Jones, 1971). When human subjects are given a choice between marijuana cigarettes with different THC concentrations, those with higher THC content are preferred over those containing lower THC concentrations (Chait and Zacny, 1992; Kelly et al., 1997), in support to the role of THC as the primary psychoactive ingredient of marijuana. Accordingly, experienced marijuana users would titrate their drug intake according to THC concentrations, in order to achieve an “optimal” subjective state (Cappell et al., 1973). Interestingly, marijuana self-administration in humans can be altered by the availability of alternative reinforcers such as money or snacks (Haney et al., 1997; Ward et al., 1997).

Finally, animal models of reinstatement are used to study relapse to drug-seeking and drug-taking behavior following a period even prolonged of drug abstinence. These protocols allowed investigation of this particular aspect of the addiction cycle which likely represents the core problem of the detoxification process, compulsive drug-seeking and intense drug craving often leading to the re-occurrence of drug use in abstinent patients. From an experimental point of view, animal models of reinstatement are an expansion of SA models, as animals are first trained to self-administer the drug, and then subjected to extinction of drug-taking behavior, usually obtained by substituting

the rewarding self-administered drug with neutral physiological solution, during which responding does not result any more in the contingent presentation of the drug reward. That is, animals are tested under conditions of non-reinforcement until drug-taking behavior disappears and animals reach the defined criterion of non-drug-seeking. At this point, several stimuli can be used to trigger reinstatement of extinguished drug-seeking behavior, which have been shown to be essentially of the same nature of those effective in provoking craving and relapse in humans: (i) re-exposure to the previously experienced drug, (ii) drug-associated (conditioned) cues, or (iii) stressors, such as food deprivation or mild footshocks. A stimulus is said to reinstate drug-seeking behavior if it elicits renewed responding despite the absence of any contingent reward. Intriguingly, cross-priming phenomena from one class of addictive drugs to another are commonly seen in this model and, once again, cannabinoids behave similarly to other drugs of abuse in this respect.

As assessed in reinstatement animal models, a role for the eCB system in regulating drug-seeking behavior has been unequivocally demonstrated. Primings with CB1-R agonists are able to resume not only extinguished self-administration of cannabinoid (Spano et al., 2004), but also that of heroin (De Vries et al., 2003; Fattore et al., 2003), cocaine (De Vries et al., 2001), and alcohol-containing solutions (McGregor et al., 2005), while blockade of CB1-Rs is able to prevent drug- and/or cue-induced reinstatement of cannabinoid (Spano et al., 2004), heroin (Fattore et al., 2005b), nicotine (De Vries et al., 2005; Shoaib, 2007), alcohol (Cippitelli et al., 2005; Economidou et al., 2006), and MDMA (Anggadiredja et al., 2004). Relapse-preventing action of CB1-R antagonists were recently confirmed in clinical trials, at least for nicotine smoking, pointing to this class of compound as innovative approach in the treatment of drug addiction (Cahill and Ussher, 2007). Preclinical studies provided a solid framework for an important role of the eCB system in the neural mechanisms regulating body weight, probably by affecting the impact of food-associated stimuli, thus extending the clinical potential efficacy of CB1-R antagonists for the treatment of food addiction (Van Gaal et al., 2005).

2.2. Neurochemical evidence

Since its introduction in the 1980s, *in vivo* microdialysis has been a popular and powerful research tool to determine modifications of various neurotransmitter extracellular concentrations in discrete brain area after acute or chronic drug treatment. Typically, a semi-permeable membrane is stereotaxically implanted into a specific brain region in a freely moving animal. Endogenous substances that are low in concentration in the dialysis buffer and that possess a size small enough to diffuse through the membrane, will diffuse into it and will flow through another tube to be collected. Sensitive high-performance liquid chromatography (HPLC) procedures are usually employed to analyze the neurotransmitter of interest.

As mentioned before in this review, substances of abuse produce their addictive properties by primarily acting on the mesolimbic DA system that project from the VTA to the NAc (Koob, 1992; Wise, 2004). *In vivo* neurochemical studies in

rats have shown that behaviorally relevant doses of the most commonly abused drugs produce an extended increase in extracellular DA levels in brain reward axon terminal loci and particularly in the NAc (Di Chiara and Imperato, 1988). For several years, this thought has been a subject of debate with regard to THC and cannabinoids, until Gardner's group showed that systemic administration of THC dose-dependently enhances DA extracellular concentrations in the striatum, PFC and NAc of rats (Ng Cheong Ton et al., 1988; Chen et al., 1990, 1991). The DA-releasing effect of CB1-R agonists in brain reward axon terminal loci has been demonstrated to be comparable to that of other drugs of abuse (i.e. cocaine, nicotine, opioids), and to satisfy the criteria to be considered a neuronal release, as it is dependent on action potentials (i.e. it is abolished by tetrodotoxin) and exocytosis (i.e. it is eliminated from the dialysates when calcium is omitted from the ringer) (Gardner, 2002).

However, discrepant results were also reported, as in the same years Castañeda et al. (1991) were unsuccessful to find any modifications in DA dialysate samples obtained from both striatum and NAc using the same experimental conditions with the only exception of the route of drug administration (gavage vs. intraperitoneal) and the strain of rats (Long Evans vs. Sprague–Dawley and Lewis).

Within the NAc, the two subregions shell and core, show different afferent and efferent connections and immunohistochemical characteristics (Groenewegen and Russchen, 1984; Voorn et al., 1989; Zahm and Brog, 1992). Neurochemical (Pontieri et al., 1995; Fadda et al., 2003) and behavioral (Cardinal et al., 2002; Kelley, 2004) findings support the notion of a major role played by the shell subregion of the NAc in motivated behavior as well as in conditioned and unconditioned rewarding drug effects (Everitt and Wolf, 2002; Ikemoto and Wise, 2004; Ito et al., 2004).

In line with other drugs of abuse, it was shown that cannabinoids preferentially stimulate DA release into the shell of the NAc, as both THC and WIN 55,212-2 induce a pronounced dose-dependent effect in the shell, but only a weak response in the core after administration of high drug doses (Tanda et al., 1997). This DA-enhancing effect of cannabinoids is mediated not only by CB1-Rs, as it is specifically abolished by the CB1-R antagonist rimonabant (Tanda et al., 1997), but also by opioids receptors, as it is reversed by the unselective opioid receptor antagonist naloxone (Chen et al., 1990; Tanda et al., 1997). In addition, finding that intra-VTA injection of the μ -opioid receptor antagonist naloxonazine blocks CB1-R agonist-enhanced DA extracellular levels in the shell of the NAc, further supports a functional interaction between opioids and cannabinoids in these mesencephalic structures (Tanda et al., 1997). On the other hand, morphine does not modify DA release in the NAc of mice lacking the CB1-R (knock-out mice) whereas it dose-dependently stimulates it in the corresponding wild-type mice (Mascia et al., 1999), demonstrating that CB1-Rs regulate mesolimbic dopaminergic transmission in brain areas known to be involved in the reinforcing effects of morphine.

According to previous finding of a high degree of genetic variation in the behavioral effects of cannabinoids (Lepore et al., 1996; Deiana et al., 2007), neurochemical effects of cannabi-

noids also depend on animal strain studied (Chen et al., 1991). Indeed, since from the pioneering studies on cannabinoid administration effects on brain DA release, it has been demonstrated that low doses of THC elevated DA levels in the NAc of Lewis rats, did the same but to a lesser extent in Sprague–Dawley rats, and induced not changes in Fisher strain (Chen et al., 1991; Gardner, 2002).

More recently, it has been reported that AEA also possesses the ability to produce a fast and significant elevation in extracellular DA levels in the shell of the NAc when injected intravenously (Solinas et al., 2006, 2007b). In addition, inhibition of the fatty acid amide (FAAH) by URB597, but not inhibition of AEA transport by AM404 or UCM707, considerably potentiates both the duration and the magnitude of the AEA-induced DA rise, suggesting brain specificity for FAAH versus transport/FAAH inactivation of AEA (Solinas et al., 2006, 2007b).

Extracellular DA in the rat NAc significantly increases in response to either passive administration, i.e. given by the experimenter, or active injection, i.e. self-administered by the subject itself, of the most commonly abused drugs (Di Chiara and Imperato, 1988; Pettit and Justice, 1989).

As in the abovementioned studies, cannabinoids effect on DA extracellular levels was long investigated exclusively in animals receiving the drug passively. Few years ago, by combining intravenous self-administration procedure with *in vivo* microdialysis technique we measured fluctuations of DA levels in the NAc of rats during voluntary WIN 55,212-2 intake (Fadda et al., 2006). In this study we demonstrated that self-administered doses of intravenous WIN 55,212-2 increase DA release to a similar extent in the NAc shell of Lister Hooded and Long Evans rats, with a significant relationship between extracellular DA levels and bar-pressing rates, thus providing a reasonable neurochemical basis for the reinforcing effects of cannabinoid (Fadda et al., 2006).

Generally, neurochemical studies investigating the role of CB1-R agonist administration in drug reward and addictive behavior are focused on DA release in the NAc, in view of a putative increased electrical activity of DA neurons in the VTA. However, the enhanced DA release in the NAc could be not the result of a direct effect on DA cells, but rather the result of an indirect action on glutamatergic and GABAergic terminals impinging on DA neurons (Marinelli et al., 2007; Wenger et al., 2003). Less numerous but as much interesting are studies reporting effects of cannabinoid administration on GABA, glutamate, NE and Ach release in several brain area, such as the PFC, the striatum, the hippocampus, that are all related to emotional and/or cognitive functions (Degroot and Nomikos, 2007).

2.3. Electrophysiological evidence

Electrophysiological studies on neural mechanisms underlying addiction to cannabinoids and the involvement of the eCB system in drug abuse and reward have been focused mainly on mesolimbic DA neurons, the NAc, and associated limbic structures.

The eCB system has emerged as an important modulator of the DA neurons. Exogenous cannabinoid agonists stimulate the activity of mesencephalic DA neurons (French et al., 1997; Gessa et al., 1998). Both THC and synthetic CB1-R agonists dose-dependently enhance firing rate and bursting activity of DA neurons in the VTA, whereas their actions on DA neurons in the *pars compacta* of the substantia nigra (SNc) are less pronounced. Enhanced electrical activity translates into an increase in DA release in terminal regions, such as the NAc (Tanda et al., 1997; Pistis et al., 2002b; Cheer et al., 2004; Fadda et al., 2006) and the PFC (Chen et al., 1990, 1993; Pistis et al., 2002a). Under this aspect, cannabinoids display effects largely similar to those of other drugs of abuse belonging to different classes. Indeed, drugs abused by humans enhance DA transmission by diverse mechanisms, i.e. by enhancing firing rate of DA neurons and DA release in the NAc, such as alcohol, nicotine, GHB, opioids and cannabinoids (Matthews and German, 1984; Gessa et al., 1985; Mereu et al., 1987; Di Chiara and Imperato, 1988; Pistis et al., 2005), or by directly acting at dopaminergic terminals, such as cocaine and amphetamine (Di Chiara and Imperato, 1988; Einhorn et al., 1988). On the other hand, during withdrawal from chronic cannabinoid treatment, DA neurons display a reduced baseline activity (Diana et al., 1998), which is an additional trait in common with other drugs of abuse, such as alcohol and morphine (Diana et al., 1993, 1995).

Cannabinoid agonists most probably do not directly activate DA cells, since CB1-R or mRNA levels in the VTA and in the SNc are very low or undetectable (Herkenham et al., 1991; Matsuda et al., 1993). In fact, neurons from different areas projecting to VTA or SNc possess relatively large amounts of CB1 receptor mRNA, namely the glutamatergic neurons in the PFC and in the subthalamic nucleus (STN), or the GABAergic neurons in the striatal complex as well as in the *pars reticulata* of the substantia nigra (SNr) (Marsicano and Lutz, 1999; Matsuda et al., 1993). Thus, it is presumed that low levels of CB1-Rs are located on glutamatergic and GABAergic terminals impinging on DA neurons (Wenger et al., 2003; Marinelli et al., 2007), where they can finely regulate the release of inhibitory and excitatory neurotransmitters and DA neuron activity.

Consistently, *in vitro* electrophysiological experiments have provided evidence that CB1-R agonists depress inhibitory and excitatory post-synaptic currents recorded from DA neurons (Szabo et al., 2002; Melis et al., 2004b; Marinelli et al., 2007). The presence of CB1-Rs strongly suggested a physiological role of the eCB system in modulating synaptic functions. Hence, patch-clamp studies demonstrated that DA neurons release ECs as retrograde messengers in a Ca^{2+} -dependent manner (Melis et al., 2004a; Riegel and Lupica, 2004) during depolarization of the cell (Melis et al., 2004b), stimulation of excitatory afferents (Melis et al., 2004a), induction of burst firing *in vivo* (Melis et al., 2004a) and *in vitro* (Riegel and Lupica, 2004). Under these circumstances, released ECs transiently modulate presynaptically afferent activity and suppress incoming inputs, thus inducing neuroprotective effects (Melis et al., 2006; Melis and Pistis, 2007), or forms of synaptic depression such as depolarization-induced suppression of excitation (DSE) and depolarization-induced suppression of inhibition

(DSI) (Yanovsky et al., 2003; Melis et al., 2004b; Riegel and Lupica, 2004). Among different endocannabinoids, 2-AG, and not AEA, is the most likely messenger in synaptic modulation in DA neurons (Melis et al., 2004a, 2006). The functional consequences of eCB signalling in DA neurons are not completely understood yet. One hypothesis is that the eCB system regulates firing and pattern activity of DA neurons.

These cells fire *in vivo* in two main different patterns of activity: regular pace-maker-like activity and burst firing (Grace and Bunney, 1983), this latter being more efficacious than the former in releasing DA in the NAc (Gonon, 1988). Thus, the functional efficacy of DA neurons crucially depends on firing pattern (bursting vs. regular) rather than on the simple average firing frequency. In turn, firing rate and pattern of DA neurons depend on the activity of excitatory and inhibitory inputs (Marinelli et al., 2006), so that a feedback control of these inputs (such as that exerted by ECs) is crucial for normal functioning of DA neurons. Switching from regular to burst firing can be triggered by behavioral stimuli such as reward prediction error (Schultz, 1998, 2002, 2006; Schultz and Dickinson, 2000). Thus, the finding that ECs may be released during burst of DA neurons, similar to those caused by behaviorally salient events, appears particularly remarkable, since these molecules may have an important role in modulating signal-to-noise ratio of DA neuron activity, especially during emotional processing and sensory perception (Laviolette and Grace, 2006). Indeed, exogenous cannabinoids may profoundly affect emotional and sensory perception as well as motivation and reward by co-opting these finely regulated physiological mechanisms.

3. Circuit mechanisms contributing to cannabinoid addiction

On the basis of more than two decades of behavioral, neurochemical and electrophysiological studies, it is clear that cannabinoids have multiple potential sites of action, both within and outside the VTA, and act through different mechanisms within the multifaceted brain's reward circuitry.

Finding of colocalization of immunoreactivity for the CB1-R and for the DA synthesizing enzyme tyrosine hydroxylase, commonly used as a cellular marker for the presence of DA neurons (Wenger et al., 2003), led to the hypothesis of a CB1-R mediated direct action of cannabinoid agonists on VTA DA neurons. However, it is recognized now that VTA DA neurons are unlikely to express CB1-Rs (Matsuda et al., 1993; Julian et al., 2003), thus leading researchers to put forward new indirect mechanisms of action for cannabinoids in the brain.

CB1-R activation may in fact increase local VTA DA neuronal activity by altering the balance between the GABA inhibitory inputs on VTA DA neurons (through activation of CB1-Rs present on axon terminals of GABAergic VTA neurons) and the glutamatergic synaptic transmission from PFC neurons projecting to the VTA and NAc. In addition to its action on mechanisms common to other drugs of abuse (Johnson and North, 1992), the eCB system may participate in the addictive properties of cannabinoids and other addictive drugs by permitting the effects of these drugs on mesolimbic DA transmission.

Indeed, ECs are released in the VTA following an increment in the firing rates of DA neurons and stimulation of excitatory afferents (Melis et al., 2004b; Lupica and Riegel, 2005), which would explain the role of the eCB system in the modulation of the primary rewarding effects of cannabinoids, opioids, nicotine and alcohol, but not psychostimulants (i.e. cocaine) which instead increase DA levels in the NAc by directly acting on DA axon terminals.

Parallel DA-independent mechanisms may also be engaged by CB1-Rs activation, involving, for example, CB1-Rs present in the PFC, a brain area integrating sensory information, emotional processing and hedonic experience, which would explain the involvement of the eCB system in the motivation to seek the drug. A complementary different mechanism would give explanation for the general role of the eCB system in the reinstatement of drug-seeking behavior, probably by modulating synaptic plasticity in those brain areas (i.e. NAc, PFC, amygdala, hippocampus) underlying reward-related memories, thus consolidating the reward-driven behavior required to establish addictive processes.

4. Concluding remarks and future perspective

Identifying the nature of cannabinoid action in the brain is crucial in the optimization of potential benefit of cannabinoid-based medications as well as in developing treatment strategies for individuals attempting to quit marijuana smoking. The presence of the eCB system in reward circuits and its role in the control of motivational and emotional homeostasis suggest that drugs able to modulate cannabinoid brain signaling may serve as therapeutic tools in drug addiction.

The last decade of research on cannabinoids has led to the discovery of multiple eCB molecules in the brain, the individuation of their synthesis and degradation mechanisms, and their action as retrograde messengers. However, regardless of the enormous conceptual advances made in recent years, we still have to precisely map the brain sites that make cannabinoid drugs rewarding and able to induce dependence. The intimate brain mechanisms and substrates through which the eCB system regulates reward and addiction processes and interacts with other brain neurotransmitters are still to be identified.

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