Chapter 12. Cannabinoids and drug addiction

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CHAPTER

Cannabinoids and drug addiction

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DRUG ABUSE AND ADDICTION

Addiction is defined as obsessive thinking and compulsive need for something, like drugs, food or sex, despite the resulting negative consequences. In physiological conditions, the brain reward system reinforces behaviors required for species survival, including sexual activity, nursing, and eating. Drug abuse hijacks such a neural pathway and replaces normal reward-related behavior, leading over time to uncontrollable drug seeking and taking and, ultimately, to drug addiction. Yet, engaging in non-drug-related activities involving "natural" rewards such as food, sex, and playing activity could also activate the brain "pleasure circuit" and result in addiction. While it is quite intuitive to distinguish chemical from behavioral addictions, other important conceptual distinctions are necessary.

The terms "drug abuse," "addiction," and "dependence" are not interchangeable and cannot be used as synonyms, although they represent different ends of the same disease process.

While drug abuse refers to the taking of drugs for non-medical purposes, typically because of the drug's positive subjective effects, "drug addiction" develops after repeated substance use and normally includes a pressing urge to take the drug and difficulties in controlling its consumption. Clinically, the occasional but limited use of a drug is different from escalated drug use and the emergence of chronic drug dependence. Yet, for some individuals drug addiction develops over time and usually begins with misuse, moving toward abuse and resulting in addiction (Figure 12.1). Once addicted, many drug users feel completely powerless and persevere in using the drug in the face of potentially dangerous health consequences.

Drug addiction is a chronically relapsing disorder characterized by (1) compulsion to seek and take the drug, (2) loss of control in limiting drug intake despite harmful consequences, (3) emergence of a withdrawal state and negative emotional

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FIGURE 12.1

Different phases of the human addiction cycle.

state (e.g., dysphoria, irritability, anxiety) when access to the drug is prevented, (4) greater importance given to obtaining the drug than to other activities or goals, and (5) development of tolerance. Addiction involves a complex neuropharmacologic behavioral cycle in which positive reinforcement exerted by the drug and the negative state of withdrawal drive the user to extremes to obtain the drug. Conversely, *drug dependence* refers to the need to continue taking a drug to avoid withdrawal effects on drug discontinuation, and is not necessarily associated with the rewarding properties of the drug nor is related to its abuse liability. Several drugs, such as the selective serotonin reuptake inhibitors (SSRIs), can induce dependence but do not possess positive reinforcing properties.

Closely linked to the concept of drug dependence, drug *withdrawal* (e.g., abstinence) is caused by chronic drug use cessation, is characterized by signs and physical symptoms usually opposite to the acute effects of the drug, and is associated with the emergence of negative emotional feelings. Even if it is possible for drug addicts to desist from drug use, maintaining abstinence is extremely difficult. The inability to remain abstinent is often referred to as *relapse* and consists of a process by which an abstaining individual falls again into old behavioral patterns and substance use, i.e., the return to drug use after a period of withdrawal. Relapse is the most common outcome of recovery programs treating addictive behaviors, for which *craving* (i.e., the strong, often uncontrollable desire to use the drug) represents a major risk factor. At the clinical level, craving and relapse are now considered major challenges in drug addiction treatment, and preventing relapse when an abstinent patient is exposed to the drug or drug-related stimuli is still demanding.

Table 12.1 Factors Triggering Relapse in Both Humans and Animals

	Humans	Animals
Drug priming	A single exposure to the previously abused drug	Not contingent, not reinforced acute drug injection
Environmental cues	People, places or things associated with past drug use	Context, cue light or tone previously associated with drug delivery
Stress	Divorce	Intermittent footshock
	Loss of employment or beloved person	Acute 1 day food deprivation
	Violence	Yohimbine (chemical stress)
	Negative or challenging emotions	

In human drug users, a variety of events or stimuli can precipitate drug craving and elicit the urge to use the drug, which ultimately results in relapse in abstinent individuals. The presentation of the drug itself, or stimuli previously associated with drug delivery (e.g., place, people, paraphernalia) or stressful events (e.g., loss of beloved person or employment, divorce), all increase the motivation to engage in drug taking and the likelihood of relapse (Bossert et al., 2013). Likewise, the same conditions that trigger relapse in humans are also able to reinstate drug-seeking behavior in laboratory animals, and include small doses of the drug itself, environmental stimuli (e.g., visual cues) previously associated with the drug delivery, and exposure to stressors such as electrical footshock or food deprivation (Shaham et al., 2003). Table 12.1 illustrates different factors triggering relapse in humans and drug-seeking reinstatement in laboratory animals.

THE MODULATING ROLE OF THE ENDOCANNABINOID SYSTEM IN DRUG-INDUCED REWARD

Cannabis is the most commonly abused illegal drug in the world and its main psychoactive ingredient, Δ^9-tetrahydrocannabinol (THC), produces rewarding effects in humans (Hart et al., 2005), non-human primates (Tanda et al., 2000), and rodents (Braida et al., 2004). Over the last two decades, an endogenous system comprised of cannabinoid type 1 (CB_1) and type 2 (CB_2) receptors, several endogenous ligands (i.e., endocannabinoids) and enzymes responsible for their synthesis and degradation have been discovered and partially characterized (see elsewhere in this book).

Pleasurable behaviors such as sexual activity, eating, nursing, parenting, social interactions, and play activity are conserved strongly in evolution, are essential

for development and survival, and represent pleasant experiences with a high reward value. As such, they can act as robust rewarding stimuli in both humans and animals. Remarkably, rewarding behaviors activate the same brain circuits that mediate the positive reinforcing effects not only of drugs of abuse but also those of other forms of addiction, such as pathological gambling and food addiction. For decades, the dopaminergic and opioid endogenous systems have been considered the most important neurotransmission systems in mediating brain reward processes. Yet, given the involvement of the endocannabinoid system in a variety of physiological functions at both the central and peripheral level, it is not surprising that it takes part in the complex machinery that regulates gratification and perception of pleasure (Fattore et al., 2010a).

Experimental findings strongly suggest a major involvement of the endocannabinoid system in general brain reward functions including drug abuse, as natural and synthetic cannabinoids and endocannabinoids can produce rewarding effects in humans and laboratory animals (Fattore et al., 2001; Hart et al., 2005; Justinova et al., 2005; Seely et al., 2012). Accordingly, cannabinoid CB_1 receptors are present in brain areas involved in reward processes, and their activation by endogenous, plant-derived or synthetic agonists produces rewarding effects *per s*e and also increases those of drugs of abuse (Vlachou and Panagis, 2014). Conversely, pharmacological or genetic blockade of cannabinoid CB_1 receptors reduces the rewarding effects of drugs of abuse and prevents their activation of dopaminergic neurotransmission (Cossu et al., 2001; Le Foll and Goldberg, 2005). Brain levels of the two best characterized endocannabinoids, anandamide and 2-arachidonoylglycerol (2-AG), are altered either by rewarding activity (Fattore et al., 2010a) or drugs of abuse (Basavarajappa et al., 2000; Viganò et al., 2003; Cippitelli et al., 2008). However, discrepant data concerning the facilitatory role played by the endocannabinoid system in brain stimulation reward have also been reported (Sañudo-Peña et al., 1997; Cheer et al., 2000). Actually, the influence of the endocannabinoid system on brain reward processes has been hypothesized to depend on the degree of activation of the different brain areas involved and to represent a mechanism for fine-tuning dopaminergic activity (Perra et al., 2005; Pillolla et al., 2007; Melis and Pistis, 2012). Notably, the endocannabinoid system appears to be also involved in the ability of drugs and drug-associated cues to reinstate drug-seeking behavior in animal models of relapse (Fattore et al., 2007a,b). Indeed, CB_1 receptor stimulation may elicit relapse not only to cannabinoid seeking (Spano et al., 2004; Fattore et al., 2010b) but also to heroin (De Vries et al., 2003; Fattore et al., 2003, 2005b) and nicotine seeking (Gamaleddin et al., 2012), all effects that are significantly attenuated, when not fully prevented, by pretreatment with the CB_1 receptor antagonist rimonabant. However, corroborating data on the involvement of the cannabinoid system in stress-induced reinstatement are still rather scarce (Vaughn et al., 2012).

ASSOCIATED POLYMORPHISMS IN THE CANNABINOID CB_1 RECEPTOR (*CNR1*) AND FATTY-ACID AMIDE HYDROLASE (*FAAH*) GENES

Many works have repeatedly associated substance dependence and drug-related behaviors with polymorphisms in the *CNR1* and *FAAH* genes (López-Moreno et al., 2012). *CNR1* is located on chromosome 6 in the 6q15 cytogenetic band and encodes a seven-transmembrane domain protein of 472 amino acids, whereas *FAAH* is located on chromosome 1 in the 1p33 cytogenetic band and encodes one transmembrane domain protein of 579 amino acids. A number of mutations described in these genes lead to altered mRNA stability and transcription rate or to a reduction of the activity of the encoded protein. Increasing evidence shows that these functional mutations are related to marijuana, cocaine, alcohol, heroin, and nicotine dependence (Hoenicka et al., 2007; Proudnikov et al., 2010; Bidwell et al., 2013).

One of the most compelling associations is with the C385A single nucleotide polymorphism (SNP), which is found in the human *FAAH* gene (385C to A) and in homozygous form is over-represented in subjects with problem drug use. This SNP, which converts a conserved proline residue in FAAH to threonine (P129T), suggests a potential link between functional abnormalities in the endocannabinoid system and drug abuse (Tyndale et al., 2007).

Another SNP in *CNR1*, rs2023239, has been associated with cannabis dependence diagnosis and intermediate phenotypes, including abstinence-induced withdrawal, cue-elicited craving, and parahippocampal activation to cannabis cues (Schacht et al., 2012). The rs2023239 G allele was shown to predict lower volume of bilateral hippocampi among cannabis users relative to controls, suggesting that *CNR1* rs2023239 variation may predispose smaller hippocampal volume after heavy cannabis use (Schacht et al., 2012).

CB_1 RECEPTOR AND FAAH KNOCKOUT MICE IN CANNABINOID ADDICTION RESEARCH

The involvement of the endocannabinoid system in drug addiction was initially studied by a pharmacological approach, i.e., the use of compounds with different affinities for cannabinoid CB_1 or CB_2 receptors or for the enzymes involved in endocannabinoid inactivation. Genetically modified mice with selective mutations in specific components of the endocannabinoid system have been generated, which allowed essential progress in establishing the specific contribution of each component to drug addiction. In particular, mice lacking the CB_1 receptor or the enzyme responsible for catabolism of the endocannabinoid anandamide, i.e., fatty-acid amide hydrolase (FAAH), represent critical tools for the identification of the CB_1 receptor and anandamide as potential targets for drug addiction treatment.

As consequences of CB_1 receptor inactivation, CB_1 receptor knockout (CB1-KO) mice do not respond to cannabinoid drugs in the classical tetrad of behavioral test, demonstrating the exclusive role of the CB_1 receptor in mediating analgesia, hypothermia, hypolocomotion, and hypotension (Ledent et al., 1999). Also reinforcement resulted the number of affected, as CB1-KO mice do not self-administer CB_1 receptor agonists nor morphine (Ledent et al., 1999), while they readily self-administer cocaine, amphetamine, and nicotine to the same extent as in wild-type (WT) mice (Cossu et al., 2001). Yet, nicotine was reported to be unable to induce conditioned place preference (CPP) in CB1-KO mice (Castañé et al., 2002). CB_1 receptors were also shown to play an important role in alcohol preference, dependence, and stress-stimulated ethanol drinking, as CB1-KO mice fail to develop a clear alcohol CPP, display significantly lower baseline alcohol consumption compared to WT mice (Houchi et al., 2005; Thanos et al., 2005), and do not display ethanol withdrawal symptoms (Racz et al., 2003). Moreover, CB_1 receptors appear to be critical for the consolidation of cocaine reinforcement and, although to a lesser extent, for its acute rewarding effects (Soria et al., 2005). When compared to WT mice, CB1-KO animals display a significant reduction in the breakpoint level for cocaine self-administration under a progressive-ratio (PR) schedule of reinforcement (Xi et al., 2011). They also show reduced motor and striatal signaling responses to cocaine and amphetamines, and altered cocaine-induced sensitization (Corbillé et al., 2007).

These mutant mice were useful to also appreciate the involvement of the endocannabinoid system in the reinforcing effects of 3,4-methylenedioxymethamphetamine (MDMA). In fact, CB1-KO mice not only are less responsive than WT mice to the stimulating effect of MDMA on locomotor activity, body temperature, and anxiogenic-like responses, but they also fail to self-administer MDMA (Touriño et al., 2008), and do not develop sensitization to the locomotor stimulant effects of amphetamine (Thiemann et al., 2008).

The involvement of the CB_1 receptor in drug-induced reward may be ascribed, at least in part, to the general modulatory role of the endocannabinoid system in hedonic reward perception and processing (Friemel et al., 2014). In support of this, CB2-KO mice (1) do not develop nicotine CPP (Ignatowska-Jankowska et al., 2013), (2) do self-administer significantly less nicotine than WT mice, and (3) do not exhibit somatic signs of nicotine withdrawal (Navarrete et al., 2013). Moreover, deletion of CB_1 receptors decreases operant behavior and motivation to obtain highly palatable isocaloric food in mice, without affecting the operant responses to obtain standard pellets (Guegan et al., 2013). Notably, cannabinoid receptor-dependent changes in drug- and food-oriented appetitive behaviors may reflect more general changes in reward-learning processes, including those whereby the incentive value of the drug or food is assigned to instrumental outcomes or outcome-associated stimuli. Accordingly, CB1-KO mice show significant deficits in outcome-selective instrumental devaluation (Crombag et al., 2009), suggesting a crucial role for the CB_1 receptor in the capability to represent

and use sensory-specific outcome representations to alter appetitive behaviors. In line with this hypothesis, a reduced sensitivity to reward in CB1-KO mice has been described (Sanchis-Segura et al., 2004).

Genetic deletion of *FAAH* is associated with a pattern of intense CB_1 receptor-dependent behavioral responses, including hypomotility, analgesia, catalepsy, and hypothermia (Cravatt et al., 2001). Mice lacking this enzyme display (1) less severe THC precipitated withdrawal responses (Schlosburg et al., 2009), (2) an enhanced expression of nicotine CPP, (3) exacerbated physical somatic signs of spontaneous nicotine withdrawal, and (4) an increased conditioned place aversion (CPA) in a mecamylamine-precipitated model of nicotine withdrawal (Merritt et al., 2008). In line with the notion that the brain endocannabinoid system is critically involved in the neural circuitry regulating alcohol consumption and motivation to consume alcohol, FAAH-KO mice also show higher selective preference for, and higher intake of, alcohol than WT littermates (Blednov et al., 2007) as well as a reduction in the severity of handling-induced convulsions following withdrawal from chronic ethanol exposure (Vinod et al., 2008). Importantly, repeated anandamide administration in FAAH-KO mice causes smaller CB_1 receptor down-regulation and desensitization and shows lesser dependence liability than repeated THC (Falenski et al., 2010), which suggests that pharmacotherapies targeting endocannabinoid degrading enzymes are less likely to cause development of tolerance and dependence than direct CB_1 receptor stimulation.

When comparing findings from FAAH-KO mice with those from CB1-KO mice the increasing endogenous cannabinoid level amplifies, while lack of CB_1 receptor signaling lessens, nicotine reward and withdrawal. In support of this, a decreased cortical FAAH expression and elevated endocannabinoid transmission were observed in alcohol-preferring (AA) rats as compared with non-preferring (ANA) rats, which were accompanied by a compensatory down-regulation of CB_1 receptor signaling (Hansson et al., 2007).

THE ENDOCANNABINOID SYSTEM IN HUMAN DRUG ADDICTION

The endocannabinoid system is involved in reward mechanisms that facilitate the hedonic value of natural (Kirkham, 2003; De Luca et al., 2012) and drug (Fattore et al., 2008) rewards. This system participates in the primary rewarding effects of cannabinoids, nicotine, alcohol, and opioids (mostly through the release of endocannabinoids in the ventral tegmental area), and in the common mechanisms underlying drug addiction and relapse to drug-seeking behavior (by also mediating the motivational effects of drug-related environmental stimuli). In turn, many drugs of abuse, including cannabinoids, opioids, alcohol, and nicotine, can alter differently the levels of endocannabinoids in selected brain regions.

In rats chronically exposed to opiates, nicotine, ethanol, or cocaine, different changes in the brain contents of endocannabinoids and CB_1 receptor levels have been described. In particular, alcohol and nicotine increased anandamide levels in the limbic forebrain (González et al., 2004b; Buczynski et al., 2013), while chronic morphine modulated the contents of 2-AG in the rat brain (Viganò et al., 2003).

In humans, recent studies have revealed diverse response by the endocannabinoid system to long-term exposure to several drugs of abuse, and cannabis, ethanol, opioids, nicotine, and cocaine were found to alter the endocannabinoid system regardless of their diverse pharmacological mechanism of action. This section of the chapter will explore clinical evidence of the alterations of the endocannabinoid system induced by the consumption of drugs of abuse.

CANNABIS

According to the last World Drug Report, cannabis is still the most widely used illicit drug worldwide (UNODC, 2013). A new generation of potent synthetic cannabinoids, which can induce serious health risks, have recently been reported in virtually all European countries (EMCDDA, 2013), and are dominating the US market under the brand names of "K2" or "Spice" (Fattore and Fratta, 2011; Seely et al., 2012). Cannabis induces dependence less readily than the majority of other illicit drugs. Yet, about 9% of marijuana users become dependent, and this proportion increases up to 17% among individuals who initiate use at a young age, and up to 25–50% among daily users (SAMHSA, 2012). It is worth noting that 23% of all substance abuse treatment admissions in the United States are for cannabis-related disorders, second only to alcohol-related disorders (SAMHSA, 2012).

Epidemiological studies have demonstrated that chronic non-medical cannabis use can lead to severe adverse health effects such as dependence syndrome, impaired respiratory function, cardiovascular diseases, adverse effects on adolescent psychosocial development and mental health, and residual cognitive impairment (Hall and Degenhardt, 2009, 2014). For these reasons, alterations in endocannabinoid signaling have been extensively examined. It was found that after cannabis use, CB_1 or CB_2 receptor mRNA (Nong et al., 2002; Rotter et al., 2013) are increased in peripheral blood cells, and that 2-AG cerebrospinal serum levels are also increased while anandamide is absent (Morgan et al., 2013). Consistent with this study, among healthy people who had not used cannabis significantly in their lives (<five times) and those who were low-frequency users (<50 times in their lifetime) no differences in anandamide levels were observed (Leweke et al., 2007), suggesting that at least low-level cannabis use does not down-regulate endocannabinoid signaling. Another clinical study showed that in peripheral blood cells serum anandamide and CB_2 receptor mRNA, but not CB_1 receptor mRNA, are increased in high frequency users (who had smoked marijuana ≥20 times but had abstained from cannabis for ≥6 months) compared with no or infrequent (≤five times lifetime) cannabis use (Muhl et al., 2014). However, animals showed a depletion of anandamide following repeated THC administration (Di Marzo et al., 2000).

During frequent cannabis use a series of poorly understood neuroplastic changes occur, which lead to the development of dependence. Cannabis withdrawal in heavy users is commonly followed by increased anxiety, insomnia, loss of appetite, migraine, irritability, and restlessness (Haney, 2005). Tolerance to cannabis and cannabis withdrawal symptoms are believed to be the result of the desensitization of CB_1 receptors by THC. Abstinence in cannabinoid-dependent individuals elicits withdrawal symptoms that promote relapse into drug use, suggesting that pharmacological strategies aimed at alleviating cannabis withdrawal might prevent relapse and reduce dependence.

Cannabinoid replacement therapy and CB_1 receptor antagonism are two potential treatments for cannabis dependence that are under investigation (Huestis et al., 2001; Allsop et al., 2014). However, abuse liability and adverse side effects may limit the value of these approaches. A potential alternative stems from the recognition that (1) frequent cannabis use may cause an adaptive down-regulation of the brain endocannabinoid signaling, and (2) that genetic traits that favor hyperactivity of the endocannabinoid system in humans may decrease susceptibility to cannabis dependence. Altogether, these findings suggest that pharmacological agents that elevate the levels of the endocannabinoids in the brain might alleviate cannabis withdrawal and dependence. One such agent, the FAAH inhibitor URB597, selectively increases anandamide levels in the brain of rodents and primates. Preclinical studies showed that URB597 produces analgesic, anxiolytic-like, and antidepressant-like effects in rodents, which are not accompanied by evident signs of abuse liability, pointing to FAAH inhibitors as a possible therapeutic avenue for the treatment of cannabis withdrawal (Clapper et al., 2009).

ALCOHOL

Starting from the 1970s onward, a growing body of evidence has suggested a link between the neuropsychological effects of cannabis and ethanol consumption. Since then, the role of the brain endocannabinoid system in alcohol abuse and dependence as well as its comorbidity with mood disorders have been widely investigated (Schmidt et al., 2002; Wang et al., 2003; Vinod and Hungund, 2005; Pava and Woodward, 2012). A potential cross-tolerance to ethanol among cannabis users was corroborated by numerous studies investigating the cognitive and psychomotor effects of these two substances in humans (Jones and Stone, 1970; MacAvoy and Marks, 1975). In a clinical study conducted in adolescents with alcohol use disorders, over 70% reported use of cannabis within the past year, with a mean frequency of smoking marijuana ranging between 16 and 20 days per month (Martin et al., 1996). In turn, individuals in treatment for cannabis use disorders increased the frequency of alcohol drinking over a period of 1 year following treatment (Stephens et al., 1994). Accordingly, daily cannabis users significantly increased self-reported ethanol craving and consumption during a 2-week abstinence from marijuana (Peters and Hughes, 2010). Importantly, alcoholism often implies enhanced impulsivity and aggression that may induce suicide

(Koller et al., 2002; Conner et al., 2006; Modesto-Lowe et al., 2006). Levels of endocannabinoids and CB_1 receptors are altered in the prefrontal cortex of depressed and alcoholic suicide victims (Ashton and Moore, 2011; Erdozain et al., 2014), which further strengthens the role of the endocannabinoid signaling in alcoholism and suicide (Vinod and Hungund, 2006).

Besides the high comorbidity between alcohol use disorders and cannabis use disorders, much evidence has also been provided in support to the notion that some of the pharmacological and behavioral effects of alcohol may be mediated through the endocannabinoid signaling system. Recent studies have demonstrated a down-regulation of CB_1 receptor function and signal transduction by chronic alcohol intake, which probably results from the persistent stimulation of CB_1 receptors by the endogenous agonists anandamide and 2-AG, the synthesis of which is increased in the limbic forebrain by chronic alcohol treatment (González et al., 2002). This enhanced formation of endocannabinoids may subsequently influence the release of neurotransmitters.

DBA/2 mice, known to avoid alcohol intake, display reduced brain CB_1 receptor function, in line with other studies where the CB_1 receptor antagonist SR141716A was shown to prevent voluntary alcohol intake in rodents. Similarly, CB_1 receptor activation promoted alcohol craving, suggesting a role for the CB_1 receptor gene in excessive drinking and development of alcoholism (Basavarajappa and Hungund, 2002).

In humans, alcohol dependence has been associated with a down-regulation of CB_1 receptors, while suicide is thought to be related to the up-regulation of these receptors in the ventral striatum (Vinod et al., 2010). Besides chronic alcohol use, other studies indicate that acute consumption of a moderate amount of ethanol affects the levels of the endocannabinoids in some brain regions (Feuerecker et al., 2012). Indeed, both anandamide and 2-AG levels were found significantly reduced in healthy volunteers after consumption of a moderate amount (28 g of ethanol) of red wine (Feuerecker et al., 2012).

Accumulating evidence continues to link certain aspects of the endogenous cannabinoid system with alcohol dependence, negative-reinforcement learning, and the modulation of stress responses. Specific alterations in brain regions related to stress and negative-reinforcement learning have been reported to exist in type 1 alcoholics, which are anxiety prone and characterized by adult onset alcoholism, and in type 2 alcoholics, which are characterized by impulsive, antisocial behavior and teenage-onset alcoholism (Cloninger, 1995).

Endocannabinoids have both anxiogenic and anxiolytic properties (Bortolato et al., 2006; Moreira and Wotjak, 2010), and different brain regions seem to be responsible for the anxiogenic and anxiolytic properties of the endocannabinoids (Rubino et al., 2008). In a recent study, endocannabinoid levels were measured in the amygdala and hippocampus of type 1 and type 2 alcoholic postmortem brains, and compared with analogous samples from a group of non-alcoholic controls (Kärkkäinen et al., 2013). A statistically significant difference between the groups was found in the level of the putative endocannabinoid docosatetraenoylethanolamine

(DHEA), an ethanolamide derivative of the omega-3 fatty acid docosahexaenoic acid (DHA), in the amygdala but not in the hippocampus. Another human postmortem brain study reported significant differences only in the levels of anandamide in the NAc and cortical regions (Lehtonen et al., 2010), confirming that in human alcoholism changes in 2-AG brain content may not be as important as suggested by animal studies (González et al., 2002, 2004b; Rubio et al., 2007, 2009; Malinen et al., 2009).

Notably, recent studies have suggested a possible protective effect of cannabidiol (CBD) in cannabis withdrawal syndrome and adverse psychological effects (Niesink and van Laar, 2013). A recent study described the case of a young woman with cannabis withdrawal syndrome treated with CBD for 10 days (Crippa et al., 2013). Daily symptom assessments demonstrated the absence of significant withdrawal, anxiety, and dissociative symptoms during the treatment.

NICOTINE

Nicotine is the primary psychoactive compound of tobacco smoke, and it determines and maintains tobacco dependence. Several lines of evidence suggest a functional interaction between central cholinergic and endocannabinoid systems (Castañé et al., 2005; Maldonado et al., 2006). Epidemiological, pharmacological, and behavioral studies in humans point out a clear link between cannabis and nicotine abuse (Viveros et al., 2006). Accordingly, many animal studies have shown that the pharmacological manipulation of the elements of the endocannabinoid system strongly influence important aspects of nicotine dependence (Scherma et al., 2008).

For example, CB_1 receptor activation and inhibition enhances and attenuates respectively the rewarding effects of nicotine, and nicotine addiction has been associated with altered endocannabinoid modulation of reward processing in the nucleus accumbens (Jansma et al., 2013). However, while FAAH inhibition results in increased brain anandamide levels and therefore increased endocannabinoid tone, distinct effects of FAAH inhibition on nicotine reward have been reported in mice and rats (Muldoon et al., 2013). A major PPAR-α receptor component appears to mediate the anti-nicotine reward effects of FAAH inhibitors in rats (Mascia et al., 2011).

In rats, nicotine and endocannabinoids seem to enhance the reinforcing effects of both systems (Viveros et al., 2006), and changes in endogenous cannabinoid levels have been observed in different brain regions chronically exposed to nicotine, such as the brainstem, hippocampus, cerebral cortex, and striatum (González et al., 2002). In mice, the administration of nicotine facilitates the pharmacological responses, tolerance, and physical dependence induced by THC (Valjent et al., 2002), while CB_1 receptor agonists decrease nicotine somatic withdrawal signs in mice (Balerio et al., 2004). Furthermore, no differences were reported on the effect of FAAH inhibition in nicotine somatic withdrawal signs in mice and rats. However, differences in affective signs of withdrawal, such as anxiety and aversion, after FAAH blockade seem to be emerging. More generally, the effects of FAAH inhibitors on nicotinic behavioral responses in animals may be influenced by procedural differences, species differences, level of nicotine exposure, and degree of FAAH inhibition. These factors

are likely to play an important role in understanding the physiological function of FAAH in nicotine reward and withdrawal. Pharmacological inhibition of FAAH blocks nicotine self-administration and prevent nicotine-induced reinstatement in rats, suggesting that FAAH is a promising molecular target for tobacco dependence (Scherma et al., 2008; Muldoon et al., 2013).

In humans, CB_1 receptor antagonists were evaluated as anti-smoking therapy, with some promising results (Cohen et al., 2005). For example, when used in combination with a nicotine patch, rimonabant was well tolerated and increased smoking cessation rates over rimonabant alone, with little weight gain after cessation in either group, even among weight-concerned smokers (Rigotti et al., 2009). However, evidence for using these antagonists in maintaining smoking abstinence remained inconclusive, mainly because of the adverse events observed, including nausea, upper respiratory tract infections and, more worryingly, depression and suicidal thoughts in people taking CB_1 receptor antagonists for weight control (Cahill and Ussher, 2007).

COCAINE

Cocaine use represents an important worldwide health problem due to the large number of physical, legal, social, cognitive, psychological, and psychiatric associated problems and comorbidity (O'Brien and Anthony, 2005; Karila et al., 2012). Cannabis is one of the most widely used illicit substances among users of psychostimulants such as cocaine and amphetamines. Interestingly, recent evidence points toward the involvement of the endocannabinoid system in the neurobiological processes related to stimulant addiction (Olière et al., 2013).

In cocaine addicts, a link between exposure to cocaine and dysregulated brain endocannabinoid signaling has been reported. Indeed, CB_1 but not CB_2 receptor protein and G-protein coupled receptor regulatory kinases (GRK) were reported to be significantly reduced in the prefrontal cortex with a simultaneous receptor redistribution and/or internalization, i.e., they were decreased in membranes and increased in cytosol (Álvaro-Bartolomé and García-Sevilla, 2013). Thus, in cocaine-addicted subjects the reductions of CB_1 receptors and GRK determines a receptor desensitization, a notion further strengthened by the finding that chronic cocaine reduces CB_1 receptor protein also in the cerebral cortex of mice and rats (Álvaro-Bartolomé and García-Sevilla, 2013).

The evaluation of plasma-free endocannabinoids and circulating endocannabinoid-related lipids in abstinent cocaine addicts can be useful for the identification of biomarkers for cocaine addiction. Pavón and colleagues (2013) found that plasma acyl derivatives are altered in abstinent cocaine-addicted subjects. In the same subjects, free N-acyl-ethanolamines were found to be increased while 2-acyl-glycerols were decreased. Intriguingly, the monounsaturated N-oleoyl-ethanolamine and N-palmitoleoyl-ethanolamine were significantly elevated in cocaine addicts diagnosed with mood and anxiety disorders when compared with non-comorbid cocaine-addicted subjects (Pavón et al., 2013).

Human studies also show that cannabinoid receptor *CNR1* gene polymorphisms might be related to cocaine addiction (López-Moreno et al., 2012). Two single nucleotide polymorphisms (SNPs) in *CNR1*, i.e., rs6454674 and rs806368, have been associated with cocaine dependence (Zuo et al., 2009; Clarke et al., 2013). Notably, also the (AAT)n triplet repeat polymorphism in the close proximity of the *CNR1* gene has been associated with predisposition to cocaine dependence (Comings et al., 1997; Ballon et al., 2006), although non-significant association data have also been reported (Covault et al., 2001; Herman et al., 2006).

From a clinical perspective, much evidence suggests that cannabinoid ligands and endocannabinoid-level enhancers may be therapeutically useful against cocaine dependence (Tanda, 2007). For example, crack cocaine abusers reported smoking cannabis in order to get relief from cocaine-withdrawal symptoms (Labigalini et al., 1999). However, caution must be used before drawing any conclusions, especially in light of the potential negative clinical implications of cannabis use in cocaine-abstinent subjects (Aharonovich et al., 2005).

AMPHETAMINES

Amphetamine and its derivatives, i.e., methamphetamine (METH) and N-methyl-3,4-methylenedioxymethamphetamine (MDMA), are stimulant drugs that increase feelings of arousal and euphoria, decrease fatigue, and enhance attention and feelings of alertness. Co-abuse of cannabis and amphetamines is very common among polydrug users in Western societies. Yet, there are only a few and somewhat contradictory studies examining the effects of smoking marijuana and concomitant use of amphetamines on cognitive parameters (e.g., impulsivity, memory, executive functions). Similarly, animal studies examining long-term effects of amphetamine and cannabinoid co-administration and underlying neurobiology are quite limited.

Ecstasy users are typically polydrug abusers, and marijuana is commonly smoked among regular ecstasy users (Sindicich et al., 2009). In ecstasy users, regular cannabis and/or METH use confers additional risk of poor mental health and high levels of psychological distress, particularly with regard to paranoia, over regular ecstasy use alone (Scott et al., 2012). Regular cannabis and METH use was also associated with earlier initiation to use ecstasy (Scott et al., 2012). Marijuana is frequently smoked also by METH abusers (Simon et al., 2002; Gonzalez et al., 2004a); yet, whether it is smoked for the purpose of enhancing METH subjective effects or attenuating its adverse effects (self-medication purposes) is still unknown. Regular cannabis abuse in METH-dependent individuals has been associated with frontal, temporal, and striatal metabolic abnormalities compared to subjects that use METH only (Voytek et al., 2005). However, cannabis use was not found to exacerbate the neurotoxic effect of METH (Gonzalez et al., 2004a). Actually, a recent animal study indicates that METH-induced neurotoxicity in the caudate putamen and PFC can be attenuated by pre- and post-treatment with THC through inhibition of nNOS overexpression and astrocyte activation (Castelli et al., 2014).

Adolescent methamphetamine and cannabis abusers were found to have increased regional striatal volume and show stronger novelty-seeking behavior as compared to healthy controls (Churchwell et al., 2012). In the same study, degree of methamphetamine exposure was found to be positively correlated with regional striatal volume and novelty seeking in methamphetamine and cannabis users. Another clinical study evaluated whether the subjective responses of healthy volunteers to controlled administration of amphetamine are influenced by polymorphisms in the FAAH gene (Dlugos et al., 2010). Genotypes at rs3766246 and rs2295633 were found to be significantly associated with increased ratings of "arousal" in response to amphetamines, suggesting that the endocannabinoid system influences variation in subjective response to amphetamines. Yet, other studies found no significant association between methamphetamine dependence and the synonymous polymorphism of the *FAAH* gene, Pro129Thr (Morita et al., 2005). Regrettably, no studies have been conducted so far to quantify the brain level of endocannabinoids in amphetamine users, or to evaluate the density and functionality of CB_1 receptor in the brains of METH or MDMA users.

OPIOIDS

Cannabinoids and opioids share several pharmacological properties, including antinociception, hypothermia, sedation, and hypotension. Currently, a great body of evidence supports similarities of actions and interactions between central opioid and cannabinoid systems with reference to drug dependence and abuse (Fattore et al., 2004, 2005a; Spano et al., 2010; Scavone et al., 2013), including relapse phenomena (Fattore et al., 2003, 2005b, 2011; Spano et al., 2004). The first evidence for such an interaction in dependence-related phenomena, e.g., reward and withdrawal, dates to the middle 1970s, when it was reported that administration of THC attenuates naloxone-induced abstinence in morphine-dependent rats (Hine et al., 1975) and mice (Bhargava, 1976), whereas rats chronically treated with cannabinoids show opioid-like withdrawal signs following acute naloxone administration (Kaymakcalan et al., 1977).

Earlier clinical studies indicated that oral or smoked THC consistently induces changes in mood, usually euphoria, while higher doses are psychotomimetic producing, for example, marked distortion in visual and auditory perception (Isbell et al., 1967). When the effects of the opioid antagonist naltrexone on subjective responses to THC were examined in marijuana users, it was found that THC increases heart rate and self-reported drug effects (i.e., euphoria, marijuana-like effects) and decreases psychomotor performance, while naltrexone increases heart rate and decreases self-reported measures of vigor and hunger but does not alter any of the effects of THC (Wachtel and de Wit, 2000). Notably, more recent studies show that in morphine abusers cannabinoid receptors are up-regulated in the periphery blood mononuclear cells and that the expression of interleukin 4 (IL-4) mRNA in these cells is higher than that in healthy people (Zhang et al., 2012),

indicating that exposure to morphine can affect the expression of cannabinoid receptors and immune functions.

Cannabis is the most prevalent type of illicit drug used among heroin addicts. This implies at least two important issues to address, i.e., to determine the potential consequences associated with cannabis use in methadone-treated patients, and to evaluate the influence of concurrent marijuana use on treatment outcomes in opioid users on maintenance treatment. Concerning the first point, it was found that marijuana use does not impact on risk behavior for contracting acquired immunodeficiency syndrome (AIDS) (Saxon et al., 1990), but it can induce abnormalities in resting respiratory functions (Teichtahl et al., 2004). Moreover, when comparing outcomes of marijuana users and non-users enrolled in a methadone-maintenance program, no relation between cannabis consumption and the use of opioids was found (Saxon et al., 1990). Importantly, chronic marijuana smoking did not affect the normalization of the hypothalamic-pituitary-adrenal (HPA) axis induced by methadone in heroin addicts (Nava et al., 2007), which further supports the notion that marijuana use is not a risk factor for treatment outcome in methadone-maintenance treatment (Seivewright, 2003; Weizman et al., 2004).

Concerning the influence of opioid drugs on the brain endocannabinoid levels, it has been established that chronic morphine modulates the contents of 2-AG in the rat brain (Viganò et al., 2003), but no specific studies have been conducted so far on human opioid addicts. Similarly, it has been demonstrated that voluntary chronic intake of opioids or cannabinoids by rats induces reciprocal but differential regulation of mu-opioid and CB_1 receptor density and activity in brain structures underlying drug-taking and drug-seeking behavior (Fattore et al., 2007c), but whether or not similar effects also occur in the human brain remains to be investigated.

CONCLUSIONS

The motivational and addictive properties of drugs of abuse are mediated through drug-induced changes in neurotransmitter and neuromodulatory signaling within the brain. Endocannabinoids mediate retrograde signaling in neuronal tissues and are involved in the regulation of synaptic transmission to suppress neurotransmitter release by the presynaptic cannabinoid receptors. This powerful modulatory action on synaptic transmission has significant functional implications and interactions with the effects of abused substances. Although there are differences in the central effects caused by various classes of abused drugs, accumulating evidence indicates a central role for the ubiquitous endocannabinoid physiological control system in the regulation of the rewarding effects of these substances. Cannabinoids and endocannabinoids appear to boost the rewarding effects of addictive drugs, including alcohol, nicotine, cocaine, amphetamines, and opiates, suggesting that the endocannabinoid system may represent an important target for the treatment of addictive disorders.

REFERENCES

Aharonovich, E., Liu, X., Samet, S., Nunes, E., Waxman, R., Hasin, D., 2005. Postdischarge cannabis use and its relationship to cocaine, alcohol, and heroin use: a prospective study. Am. J. Psychiatry 162 (8), 1507–1514.

Allsop, D.J., Copeland, J., Lintzeris, N., Dunlop, A.J., Montebello, M., Sadler, C., et al., 2014. Nabiximols as an agonist replacement therapy during cannabis withdrawal: a randomized clinical trial. JAMA Psychiatry 71 (3), 281–291.

Álvaro-Bartolomé, M., García-Sevilla, J.A., 2013. Dysregulation of cannabinoid CB1 receptor and associated signaling networks in brains of cocaine addicts and cocaine-treated rodents. Neuroscience 247, 294–308.

Ashton, C.H., Moore, P.B., 2011. Endocannabinoid system dysfunction in mood and related disorders. Acta Psychiatr. Scand. 124 (4), 250–261.

Balerio, G.N., Aso, E., Berrendero, F., Murtra, P., Maldonado, R., 2004. Delta9-tetrahydrocannabinol decreases somatic and motivational manifestations of nicotine withdrawal in mice. Eur. J. Neurosci. 20, 2737–2748.

Ballon, N., Leroy, S., Roy, C., Bourdel, M.C., Charles-Nicolas, A., Krebs, M.O., et al., 2006. (AAT)n repeat in the cannabinoid receptor gene (CNR1): association with cocaine addiction in an African-Caribbean population. Pharmacogenomics J. 6 (2), 126–130.

Basavarajappa, B.S., Hungund, B.L., 2002. Neuromodulatory role of the endocannabinoid signaling system in alcoholism: an overview. Prost. Leuk. Essent. Fatty Acids 66 (2–3), 287–299.

Basavarajappa, B.S., Saito, M., Cooper, T.B., Hungund, B.L., 2000. Stimulation of cannabinoid receptor agonist 2-arachidonylglycerol by chronic ethanol and its modulation by specific neuromodulators in cerebellar granule neurons. Biochem. Biophys. Acta 1535 (1), 78–86.

Bhargava, H.N., 1976. Inhibition of naloxone-induced withdrawal in morphine dependent mice by 1-trans-delta-9-tetrahydrocannabinol. Eur. J. Pharmacol. 36, 259–262.

Bidwell, L.C., Metrik, J., McGeary, J., Palmer, R.H., Francazio, S., Knopik, V.S., 2013. Impulsivity, variation in the cannabinoid receptor (CNR1) and fatty acid amide hydrolase (FAAH) genes, and marijuana-related problems. J. Stud. Alcohol Drugs 74 (6), 867–878.

Blednov, Y.A., Cravatt, B.F., Boehm 2nd, S.L., Walker, D., Harris, R.A., 2007. Role of endocannabinoids in alcohol consumption and intoxication: studies of mice lacking fatty acid amide hydrolase. Neuropsychopharmacology 32 (7), 1570–1582.

Bortolato, M., Campolongo, P., Mangieri, R.A., Scattoni, M.L., Frau, R., Trezza, V., et al., 2006. Anxiolytic-like properties of the anandamide transport inhibitor AM404. Neuropsychopharmacology 31 (12), 2652–2659.

Bossert, J.M., Marchant, N.J., Calu, D.J., Shaham, Y., 2013. The reinstatement model of drug relapse: recent neurobiological findings, emerging research topics, and translational research. Psychopharmacology 229 (3), 453–476.

Braida, D., Iosuè, S., Pegorini, S., Sala, M., 2004. Delta9-tetrahydrocannabinol-induced conditioned place preference and intracerebroventricular self-administration in rats. Eur. J. Pharmacol. 506 (1), 63–69.

Buczynski, M.W., Polis, I.Y., Parsons, L.H., 2013. The volitional nature of nicotine exposure alters anandamide and oleoylethanolamide levels in the ventral tegmental area. Neuropsychopharmacology 38 (4), 574–584.

Cahill, K., Ussher, M., 2007. Cannabinoid type 1 receptor antagonists (rimonabant) for smoking cessation. Cochrane Database Syst. Rev. (4), CD005353.

Castañé, A., Valjent, E., Ledent, C., Parmentier, M., Maldonado, R., Valverde, O., 2002. Lack of CB1 cannabinoid receptors modifies nicotine behavioural responses, but not nicotine abstinence. Neuropharmacology 43 (5), 857–867.

Castañé, A., Berrendero, F., Maldonado, R., 2005. The role of the cannabinoid system in nicotine addiction. Pharmacol. Biochem. Behav. 81 (2), 381–386.

Castelli, M.P., Madeddu, C., Casti, A., Casu, A., Casti, P., Scherma, M., et al., 2014. Δ9-tetrahydrocannabinol prevents methamphetamine-induced neurotoxicity. PLOS ONE 9 (5), e98079.

Cheer, J.F., Kendall, D.A., Marsden, C.A., 2000. Cannabinoid receptors and reward in the rat: a conditioned place preference study. Psychopharmacology 151 (1), 25–30.

Churchwell, J.C., Carey, P.D., Ferrett, H.L., Stein, D.J., Yurgelun-Todd, D.A., 2012. Abnormal striatal circuitry and intensified novelty seeking among adolescents who abuse methamphetamine and cannabis. Dev. Neurosci. 34, 310–317.

Cippitelli, A., Cannella, N., Braconi, S., Duranti, A., Tontini, A., Bilbao, A., et al., 2008. Increase of brain endocannabinoid anandamide levels by FAAH inhibition and alcohol abuse behaviours in the rat. Psychopharmacology 198 (4), 449–460.

Clapper, J.R., Mangieri, R.A., Piomelli, D., 2009. The endocannabinoid system as a target for the treatment of cannabis dependence. Neuropharmacology 56 (1), 235–423.

Clarke, T.K., Bloch, P.J., Ambrose-Lanci, L.M., Ferraro, T.N., Berrettini, W.H., Kampman, K.M., et al., 2013. Further evidence for association of polymorphisms in the CNR1 gene with cocaine addiction: confirmation in an independent sample and meta-analysis. Addict. Biol. 18 (4), 702–708.

Cloninger, C.R., 1995. The psychobiological regulation of social cooperation. Nat. Med. 1, 623–625.

Cohen, C., Kodas, E., Griebel, G., 2005. CB1 receptor antagonists for the treatment of nicotine addiction. Pharmacol. Biochem. Behav. 81 (2), 387–395.

Comings, D.E., Muhleman, D., Gade, R., Johnson, P., Verde, R., Saucier, G., et al., 1997. Cannabinoid receptor gene (CNR1): association with i.v. drug use. Mol. Psychiatry 2 (2), 161–168.

Conner, K.R., Hesselbrock, V.M., Schuckit, M.A., Hirsch, J.K., Knox, K.L., Meldrum, S., et al., 2006. Precontemplated and impulsive suicide attempts among individuals with alcohol dependence. J. Stud. Alcohol 67 (1), 95–101.

Corbillé, A.G., Valjent, E., Marsicano, G., Ledent, C., Lutz, B., Hervé, D., et al., 2007. Role of cannabinoid type 1 receptors in locomotor activity and striatal signaling in response to psychostimulants. J. Neurosci. 27 (26), 6937–6947.

Cossu, G., Ledent, C., Fattore, L., Imperato, A., Böhme, G.A., Parmentier, M., et al., 2001. Cannabinoid CB1 receptor knockout mice fail to self-administer morphine but not other drugs of abuse. Behav. Brain Res. 118 (1), 61–65.

Covault, J., Gelernter, J., Kranzler, H., 2001. Association study of cannabinoid receptor gene (CNR1) alleles and drug dependence. Mol. Psychiatry 6 (5), 501–502.

Cravatt, B.F., Demarest, K., Patricelli, M.P., Bracey, M.H., Giang, D.K., Martin, B.R., et al., 2001. Supersensitivity to anandamide and enhanced endogenous cannabinoid signaling in mice lacking fatty acid amide hydrolase. Proc. Natl Acad. Sci. USA 98 (16), 9371–9376.

Crippa, J.A., Hallak, J.E., Machado-de-Sousa, J.P., Queiroz, R.H., Bergamaschi, M., Chagas, M.H., et al., 2013. Cannabidiol for the treatment of cannabis withdrawal syndrome: a case report. J. Clin. Pharm. Ther. 38 (2), 162–164.

Crombag, H.S., Johnson, A.W., Zimmer, A.M., Zimmer, A., Holland, P.C., 2009. Deficits in sensory-specific devaluation task performance following genetic deletions of cannabinoid (CB1) receptor. Learn. Mem. 17 (1), 18–22.

De Luca, M.A., Solinas, M., Bimpisidis, Z., Goldberg, S.R., Di Chiara, G., 2012. Cannabinoid facilitation of behavioral and biochemical hedonic taste responses. Neuropharmacology 63 (1), 161–168.

De Vries, T.J., Homberg, J.R., Binnekade, R., Raasø, H., Schoffelmeer, A.N., 2003. Cannabinoid modulation of the reinforcing and motivational properties of heroin and heroin-associated cues in rats. Psychopharmacology 168 (1–2), 164–169.

Di Marzo, V., Berrendero, F., Bisogno, T., Gonzalez, S., Cavaliere, P., Romero, J., et al., 2000. Enhancement of anandamide formation in the limbic forebrain and reduction of endocannabinoid contents in the striatum of delta9-tetrahydrocannabinol-tolerant rats. J. Neurochem. 74, 1627–1635.

Dlugos, A.M., Hamidovic, A., Hodgkinson, C.A., Goldman, D., Palmer, A.A., de Wit, H., 2010. More aroused, less fatigued: fatty acid amide hydrolase gene polymorphisms influence acute response to amphetamine. Neuropsychopharmacology 35 (3), 613–622.

EMCDDA, European Monitoring Centre for Drugs and Drug Addiction, European Drug Report, 2013. Trends and Developments. Publications Office of the European Union, Luxembourg.

Erdozain, A.M., Rubio, M., Valdizan, E.M., Pazos, A., Meana, J.J., Fernández-Ruiz, J., et al., 2014. The endocannabinoid system is altered in the post-mortem prefrontal cortex of alcoholic subjects. Addict. Biol. [Epub ahead of print].

Falenski, K.W., Thorpe, A.J., Schlosburg, J.E., Cravatt, B.F., Abdullah, R.A., Smith, T.H., et al., 2010. FAAH −/− mice display differential tolerance, dependence, and cannabinoid receptor adaptation after delta 9-tetrahydrocannabinol and anandamide administration. Neuropsychopharmacology 35 (8), 1775–1787.

Fattore, L., Fratta, W., 2011. Beyond THC: the new generation of cannabinoid designer drugs. Front. Behav. Neurosci. 5, 60.

Fattore, L., Cossu, G., Martellotta, C.M., Fratta, W., 2001. Intravenous self-administration of the cannabinoid CB1 receptor agonist WIN 55,212-2 in rats. Psychopharmacology 156 (4), 410–416.

Fattore, L., Spano, M.S., Cossu, G., Deiana, S., Fratta, W., 2003. Cannabinoid mechanism in reinstatement of heroin-seeking after a long period of abstinence in rats. Eur. J. Neurosci. 17 (8), 1723–1726.

Fattore, L., Cossu, G., Spano, M.S., Deiana, S., Fadda, P., Scherma, M., et al., 2004. Cannabinoids and reward: interactions with the opioid system. Crit. Rev. Neurobiol. 16 (1–2), 147–158.

Fattore, L., Deiana, S., Spano, S.M., Cossu, G., Fadda, P., Scherma, M., et al., 2005a. Endocannabinoid system and opioid addiction: behavioural aspects. Pharmacol. Biochem. Behav. 81 (2), 343–345.

Fattore, L., Spano, M.S., Cossu, G., Deiana, S., Fadda, P., Fratta, W., 2005b. Cannabinoid CB(1) antagonist SR 141716A attenuates reinstatement of heroin self-administration in heroin-abstinent rats. Neuropharmacology 48 (8), 1097–1104.

Fattore, L., Fadda, P., Fratta, W., 2007a. Endocannabinoid regulation of relapse mechanisms. Pharmacol. Res. 56 (5), 418–427.

Fattore, L., Spano, M.S., Deiana, S., Melis, V., Cossu, G., Fadda, P., et al., 2007b. An endocannabinoid mechanism in relapse to drug seeking: a review of animal studies and clinical perspectives. Brain Res. Rev. 53 (1), 1–16.

Fattore, L., Viganò, D., Fadda, P., Rubino, T., Fratta, W., Parolaro, D., 2007c. Bidirectional regulation of mu-opioid and CB1-cannabinoid receptor in rats self-administering heroin or WIN 55,212-2. Eur. J. Neurosci. 25 (7), 2191–2200.

Fattore, L., Fadda, P., Spano, M.S., Pistis, M., Fratta, W., 2008. Neurobiological mechanisms of cannabinoid addiction. Mol. Cell. Endocrinol. 286 (1–2), S97–S107.

Fattore, L., Melis, M., Fadda, P., Pistis, M., Fratta, W., 2010a. The endocannabinoid system and nondrug rewarding behaviours. Exp. Neurol. 224 (1), 23–36.

Fattore, L., Spano, M.S., Altea, S., Fadda, P., Fratta, W., 2010b. Drug- and cue-induced reinstatement of cannabinoid-seeking behaviour in male and female rats: influence of ovarian hormones. Br. J. Pharmacol. 160 (3), 724–735.

Fattore, L., Spano, M., Melis, V., Fadda, P., Fratta, W., 2011. Differential effect of opioid and cannabinoid receptor blockade on heroin-seeking reinstatement and cannabinoid substitution in heroin-abstinent rats. Br. J. Pharmacol. 163 (7), 1550–1562.

Feuerecker, M., Hauer, D., Gresset, T., Lassas, S., Kaufmann, I., Vogeser, M., et al., 2012. Effect of an acute consumption of a moderate amount of ethanol on plasma endocannabinoid levels in humans. Alcohol Alcohol 47 (3), 226–232.

Friemel, C.M., Zimmer, A., Schneider, M., 2014. The CB1 receptor as an important mediator of hedonic reward processing. Neuropsychopharmacology 39 (10), 2387–2396.

Gamaleddin, I., Wertheim, C., Zhu, A.Z., Coen, K.M., Vemuri, K., Makryannis, A., et al., 2012. Cannabinoid receptor stimulation increases motivation for nicotine and nicotine seeking. Addict. Biol. 17 (1), 47–61.

González, S., Cascio, M.G., Fernández-Ruiz, J., Fezza, F., Di Marzo, V., Ramos, J.A., 2002. Changes in endocannabinoid contents in the brain of rats chronically exposed to nicotine, ethanol or cocaine. Brain Res. 954 (1), 73–81.

Gonzalez, R., Rippeth, J.D., Carey, C.L., Heaton, R.K., Moore, D.J., Schweinsburg, B.C., et al., 2004a. Neurocognitive performance of methamphetamine users discordant for history of marijuana exposure. Drug Alcohol Depend. 76, 181–190.

González, S., Valenti, M., de Miguel, R., Fezza, F., Fernandez-Ruiz, J., Di Marzo, V., et al., 2004b. Changes in endocannabinoid contents in reward-related brain regions of alcohol-exposed rats, and their possible relevance to alcohol relapse. Br. J. Pharmacol. 143, 455–464.

Guegan, T., Cutando, L., Ayuso, E., Santini, E., Fisone, G., Bosch, F., et al., 2013. Operant behavior to obtain palatable food modifies neuronal plasticity in the brain reward circuit. Eur. Neuropsychopharmacol. 23 (2), 146–159.

Hall, W., Degenhardt, L., 2009. Adverse health effects of non-medical cannabis use. Lancet 374 (9698), 1383–1391.

Hall, W., Degenhardt, L., 2014. The adverse health effects of chronic cannabis use. Drug Test Anal. 6 (1–2), 39–45.

Haney, M., 2005. The marijuana withdrawal syndrome: diagnosis and treatment. Curr. Psychiatry Rep. 7 (5), 360–366.

Hansson, A.C., Bermudez-Silva, F.J., Malinen, H., Hyytia, P., Sanchez-Vera, I., Rimondini, R., et al., 2007. Genetic impairment of frontocortical endocannabinoid degradation and high alcohol preference. Neuropsychopharmacology 32 (1), 117–126.

Hart, C.L., Haney, M., Vosburg, S.K., Comer, S.D., Foltin, R.W., 2005. Reinforcing effects of oral Delta9-THC in male marijuana smokers in a laboratory choice procedure. Psychopharmacology 181 (2), 237–243.

Herman, A.I., Kranzler, H.R., Cubells, J.F., Gelernter, J., Covault, J., 2006. Association study of the CNR1 gene exon 3 alternative promoter region polymorphisms and substance dependence. Am. J. Med. Genet. B Neuropsychiatry Genet. 141 (5), 499–503.

Hine, B., Friedman, E., Torrelio, M., Gershon, S., 1975. Morphine-dependent rats: blockade of precipitated abstinence by tetrahydrocannabinol. Science 187, 443–445.

Hoenicka, J., Ponce, G., Jiménez-Arriero, M.A., Ampuero, I., Rodríguez-Jiménez, R., Rubio, G., et al., 2007. Association in alcoholic patients between psychopathic traits and the additive effect of allelic forms of the CNR1 and FAAH endocannabinoid genes, and the 3′ region of the DRD2 gene. Neurotox. Res. 11 (1), 51–60.

Houchi, H., Babovic, D., Pierrefiche, O., Ledent, C., Daoust, M., Naassila, M., 2005. CB1 receptor knockout mice display reduced ethanol-induced conditioned place preference and increased striatal dopamine D2 receptors. Neuropsychopharmacology 30 (2), 339–349.

Huestis, M.A., Gorelick, D.A., Heishman, S.J., Preston, K.L., Nelson, R.A., Moolchan, E.T., et al., 2001. Blockade of effects of smoked marijuana by the CB1-selective cannabinoid receptor antagonist SR141716. Arch. Gen. Psychiatry 58 (4), 322–328.

Ignatowska-Jankowska, B.M., Muldoon, P.P., Lichtman, A.H., Damaj, M.I., 2013. The cannabinoid CB2 receptor is necessary for nicotine-conditioned place preference, but not other behavioral effects of nicotine in mice. Psychopharmacology 229 (4), 591–601.

Isbell, H., Gorodetzsky, C.W., Jesinki, D., 1967. Effects of (−)delta-9-tetrahydrocannabinol in man. Psychopharmacologia 11, 184–188.

Jansma, J.M., van Hell, H.H., Vanderschuren, L.J.M.J., Bossong, M.G., Jager, G., Kahn, R.S., et al., 2013. THC reduces the anticipatory nucleus accumbens response to reward in subjects with a nicotine addiction. Transl. Psychiatry 3, e234.

Jones, R.T., Stone, G.C., 1970. Psychological studies of marijuana and alcohol in man. Psychopharmacology 18, 108–117.

Justinova, Z., Solinas, M., Tanda, G., Redhi, G.H., Goldberg, S.R., 2005. The endogenous cannabinoid anandamide and its synthetic analog R(+)-methanandamide are intravenously self-administered by squirrel monkeys. J. Neurosci. 25 (23), 5645–5650.

Karila, L., Petit, A., Lowenstein, W., Reynaud, M., 2012. Diagnosis and consequences of cocaine addiction. Curr. Med. Chem. 19 (33), 5612–5618.

Kärkkäinen, O.K., Lehtonen, M., Laukkanen, V., Tupala, E., Hyytiä, P., Kautiainen, H., et al., 2013. Endogenous cannabinoids in amygdala and hippocampus in post-mortem brains of Cloninger type 1 and 2 alcoholics. Alcohol 47, 399–403.

Kaymakcalan, S., Ayhan, I.H., Tulunay, F.C., 1977. Naloxone-induced or postwithdrawal abstinence signs in delta9-tetrahydrocannabinol-tolerant rats. Psychopharmacology 55, 243–249.

Kirkham, T.C., 2003. Endogenous cannabinoids: a new target in the treatment of obesity. Am. J. Physiol. Regul. Integr. Comp. Physiol. 284 (2), R343–R344.

Koller, G., Preuss, U.W., Bottlender, M., Wenzel, K., Soyka, M., 2002. Impulsivity and aggression as predictors of suicide attempts in alcoholics. Eur. Arch. Psychiatry Clin. Neurosci. 252 (4), 155–160.

Labigalini Jr., E., Rodrigues, L.R., Da Silveira, D.X., 1999. Therapeutic use of cannabis by crack addicts in Brazil. J. Psychoactive Drugs 31 (4), 451–455.

Ledent, C., Valverde, O., Cossu, G., Petitet, F., Aubert, J.F., Beslot, F., et al., 1999. Unresponsiveness to cannabinoids and reduced addictive effects of opiates in CB1 receptor knockout mice. Science 283 (5400), 401–404.

Le Foll, B., Goldberg, S.R., 2005. Cannabinoid CB1 receptor antagonists as promising new medications for drug dependence. J. Pharmacol. Exp. Ther. 312 (3), 875–883.

Lehtonen, M., Storvik, M., Tupala, E., Hyytiä, P., Tiihonen, J., Callaway, J.C., 2010. Endogenous cannabinoids in post-mortem brains of Cloninger type 1 and 2 alcoholics. Eur. Neuropsychopharmacol. 20, 245–252.

Leweke, F.M., Giuffrida, A., Koethe, D., Schreiber, D., Nolden, B.M., Kranaster, L., et al., 2007. Anandamide levels in cerebrospinal fluid of first-episode schizophrenic patients: impact of cannabis use. Schiz. Res. 94 (1–3), 29–36.

López-Moreno, J.A., Echeverry-Alzate, V., Bühler, K.-M., 2012. The genetic basis of the endocannabinoid system and drug addiction in humans. J. Psychopharmacol. 26 (1), 133–143.

MacAvoy, M.G., Marks, D.F., 1975. Divided attention performance of cannabis users and non-users following cannabis and alcohol. Psychopharmacology 44, 147–152.

Maldonado, R., Valverde, O., Berrendero, F., 2006. Involvement of the endocannabinoid system in drug addiction. Trends Neurosci. 29 (4), 225–232.

Malinen, H., Lehtonen, M., Hyytiä, P., 2009. Modulation of brain endocannabinoid levels by voluntary alcohol consumption in alcohol-preferring AA rats. Alcohol Clin. Exp. Res. 33, 1711–1720.

Martin, C.S., Kaczynski, N.A., Maisto, S.A., Tarter, R.E., 1996. Polydrug use in adolescent drinkers with and without DSM-IV alcohol abuse and dependence. Alcohol Clin. Exp. Res. 20, 1099–1108.

Mascia, P., Pistis, M., Justinova, Z., Panlilio, L.V., Luchicchi, A., Lecca, S., et al., 2011. Blockade of nicotine reward and reinstatement by activation of alpha-type peroxisome proliferator-activated receptors. Biol. Psychiatry 69 (7), 633–641.

Melis, M., Pistis, M., 2012. Hub and switches: endocannabinoid signalling in mid-brain dopamine neurons. Philos. Trans. R. Soc. Lond. B Biol. Sci. 367 (1607), 3276–3285.

Merritt, L.L., Martin, B.R., Walters, C., Lichtman, A.H., Damaj, M.I., 2008. The endogenous cannabinoid system modulates nicotine reward and dependence. J. Pharmacol. Exp. Ther. 326 (2), 483–492.

Modesto-Lowe, V., Brooks, D., Ghani, M., 2006. Alcohol dependence and suicidal behavior: from research to clinical challenges. Harv. Rev. Psychiatry 14 (5), 241–248.

Moreira, F.A., Wotjak, C.T., 2010. Cannabinoids and anxiety. Curr. Top. Behav. Neurosci. 2, 429–450.

Morgan, C.J.A., Page, E., Schaefer, C., Chatten, K., Manocha, A., Gulati, S., et al., 2013. Cerebrospinal fluid anandamide levels, cannabis use and psychotic-like symptoms. Br. J. Psychiatry 202 (5), 381–382.

Morita, Y., Ujike, H., Tanaka, Y., Uchida, N., Nomura, A., Ohtani, K., et al., 2005. A non-synonymous polymorphism in the human fatty acid amide hydrolase gene did not associate with either methamphetamine dependence or schizophrenia. Neurosci. Lett. 376 (3), 182–187.

Muhl, D., Kathmann, M., Hoyer, C., Kranaster, L., Hellmich, M., Gerth, C.W., et al., 2014. Increased CB2 mRNA and anandamide in human blood after cessation of cannabis abuse. Naunyn Schmiedebergs Arch. Pharmacol. 387 (7), 691–695.

Muldoon, P.P., Lichtman, A.H., Parsons, L.H., Damaj, M.I., 2013. The role of fatty acid amide hydrolase inhibition in nicotine reward and dependence. Life Sci. 92 (8–9), 458–462.

Nava, F., Manzato, E., Lucchini, A., 2007. Chronic cannabis use does not affect the normalization of hypothalamic-pituitary-adrenal (HPA) axis induced by methadone in heroin addicts. Prog. Neuropsychopharmacol. Biol. Psychiatry 31 (5), 1089–1094.

Navarrete, F., Rodríguez-Arias, M., Martín-García, E., Navarro, D., García-Gutiérrez, M.S., Aguilar, M.A., et al., 2013. Role of CB2 cannabinoid receptors in the rewarding, reinforcing, and physical effects of nicotine. Neuropsychopharmacology 38 (12), 2515–2524.

Niesink, R.J., van Laar, M.W., 2013. Does cannabidiol protect against adverse psychological effects of THC? Front. Psychiatry 4, 130.

Nong, L., Newton, C., Cheng, Q., Friedman, H., Roth, M.D., Klein, T.W., 2002. Altered cannabinoid receptor mRNA expression in peripheral blood mononuclear cells from marijuana smokers. J. Neuroimmunol. 127 (1–2), 169–176.

O'Brien, M.S., Anthony, J.C., 2005. Risk of becoming cocaine dependent: epidemiological estimates for the United States, 2000–2001. Neuropsychopharmacology 30 (5), 1006–1018.

Olière, S., Joliette-Riopel, A., Potvin, S., Jutras-Aswad, D., 2013. Modulation of the endocannabinoid system: vulnerability factor and new treatment target for stimulant addiction. Front. Psychiatry 4, 109.

Pava, M.J., Woodward, J.J., 2012. A review of the interactions between alcohol and the endocannabinoid system: implications for alcohol dependence and future directions for research. Alcohol 46 (3), 185–204.

Pavón, F.J., Araos, P., Pastor, A., Calado, M., Pedraz, M., Campos-Cloute, R., et al., 2013. Evaluation of plasma-free endocannabinoids and their congeners in abstinent cocaine addicts seeking outpatient treatment: impact of psychiatric co-morbidity. Addict. Biol. 18 (6), 955–969.

Perra, S., Pillolla, G., Melis, M., Muntoni, A.L., Gessa, G.L., Pistis, M., 2005. Involvement of the endogenous cannabinoid system in the effects of alcohol in the mesolimbic reward circuit: electrophysiological evidence in vivo. Psychopharmacology 183, 368–377.

Peters, E.N., Hughes, J.R., 2010. Daily marijuana users with past alcohol problems increase alcohol consumption during marijuana abstinence. Drug Alcohol Dep. 106, 111–118.

Pillolla, G., Melis, M., Perra, S., Muntoni, A.L., Gessa, G.L., Pistis, M., 2007. Medial forebrain bundle stimulation evokes endocannabinoid-mediated modulation of ventral tegmental area dopamine neuron firing in vivo. Psychopharmacology 191 (3), 843–853.

Proudnikov, D., Kroslak, T., Sipe, J.C., Randesi, M., Li, D., Hamon, S., et al., 2010. Association of polymorphisms of the cannabinoid receptor (CNR1) and fatty acid amide hydrolase (FAAH) genes with heroin addiction: impact of long repeats of CNR1. Pharmacogenomics J. 10 (3), 232–242.

Racz, I., Bilkei-Gorzo, A., Toth, Z.E., Michel, K., Palkovits, M., Zimmer, A., 2003. A critical role for the cannabinoid CB1 receptors in alcohol dependence and stress-stimulated ethanol drinking. J. Neurosci. 23 (6), 2453–2458.

Rigotti, N.A., Gonzales, D., Dale, L.C., Lawrence, D., Chang, Y., CIRRUS Study Group, 2009. A randomized controlled trial of adding the nicotine patch to rimonabant for smoking cessation: efficacy, safety and weight gain. Addiction 104 (2), 266–276.

Rotter, A., Bayerlein, K., Hansbauer, M., Weiland, J., Sperling, W., Kornhuber, J., et al., 2013. CB1 and CB2 receptor expression and promoter methylation in patients with cannabis dependence. Eur. Addict. Res. 19 (1), 13–20.

Rubino, T., Guidali, C., Vigano, D., Realini, N., Valenti, M., Massi, P., et al., 2008. CB1 receptor stimulation in specific brain areas differently modulate anxiety-related behaviour. Neuropharmacology 54 (1), 151–160.

Rubio, M., McHugh, D., Fernandez-Ruiz, J., Bradshaw, H., Walker, J.M., 2007. Short-term exposure to alcohol in rats affects brain levels of anandamide, other N-acylethanolamines and 2-arachidonoyl-glycerol. Neurosci. Lett. 421, 270–274.

Rubio, M., de Miguel, R., Fernández-Ruiz, J., Gutiérrez-López, D., Carai, M.A., Ramos, J.A., 2009. Effects of a short-term exposure to alcohol in rats on FAAH enzyme and CB1 receptor in different brain areas. Drug Alcohol Depend. 99 (1–3), 354–358.

SAMHSA, Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality, 2012. The TEDS Report: Marijuana Admissions Reporting Daily Use at Treatment Entry, Rockville, MD.

Sanchis-Segura, C., Cline, B.H., Marsicano, G., Lutz, B., Spanagel, R., 2004. Reduced sensitivity to reward in CB1 knockout mice. Psychopharmacology 176 (2), 223–232.

Sañudo-Peña, M.C., Tsou, K., Delay, E.R., Hohman, A.G., Force, M., Walker, J.M., 1997. Endogenous cannabinoids as an aversive or counter-rewarding system in the rat. Neurosci. Lett. 223 (2), 125–128.

Saxon, A.J., Calsyn, D.A., Blaes, P.A., Haver, V.M., Greenberg, D.M., 1990. Marijuana use by methadone maintenance patients. NIDA Res. Monogr. 105 (1991), 306–307.

Scavone, J.L., Sterling, R.C., Van Bockstaele, E.J., 2013. Cannabinoid and opioid interactions: implications for opiate dependence and withdrawal. Neuroscience 248, 637–654.

Schacht, J.P., Hutchison, K.E., Filbey, F.M., 2012. Associations between cannabinoid receptor-1 (CNR1) variation and hippocampus and amygdala volumes in heavy cannabis users. Neuropsychopharmacology 37 (11), 2368–2376.

Scherma, M., Panlilio, L.V., Fadda, P., Fattore, L., Gamaleddin, I., Le Foll, B., et al., 2008. Inhibition of anandamide hydrolysis by cyclohexyl carbamic acid 3′-carbamoyl-3-yl ester (URB597) reverses abuse-related behavioral and neurochemical effects of nicotine in rats. J. Pharmacol. Exp. Ther. 327 (2), 482–490.

Schlosburg, J.E., Carlson, B.L., Ramesh, D., Abdullah, R.A., Long, J.Z., Cravatt, B.F., et al., 2009. Inhibitors of endocannabinoid-metabolizing enzymes reduce precipitated withdrawal responses in THC-dependent mice. AAPS J. 11 (2), 342–352.

Schmidt, L.G., Samochowiec, J., Finckh, U., Fiszer-Piosik, E., Horodnicki, J., Wendel, B., et al., 2002. Association of a CB1 cannabinoid receptor gene (CNR1) polymorphism with severe alcohol dependence. Drug Alcohol Dep. 65 (3), 221–224.

Scott, L.A., Roxburgh, A., Bruno, R., Matthews, A., Burns, L., 2012. The impact of comorbid cannabis and methamphetamine use on mental health among regular ecstasy users. Addict. Behav. 37 (9), 1058–1062.

Seely, K.A., Lapoint, J., Moran, J.H., Fattore, L., 2012. Spice drugs are more than harmless herbal blends: a review of the pharmacology and toxicology of synthetic cannabinoids. Prog. Neuropsychopharmacol. Biol. Psychiatry 39 (2), 234–243.

Seivewright, N., 2003. Methadone treatment outcomes appear mainly unaffected by cannabis use. Addiction 98, 251–252.

Shaham, Y., Shalev, U., Lu, L., De Wit, H., Stewart, J., 2003. The reinstatement model of drug relapse: history, methodology and major findings. Psychopharmacology 168 (1–2), 3–20.

Simon, S.L., Domier, C.P., Sim, T., Richardson, K., Rawson, R.A., Ling, W., 2002. Cognitive performance of current methamphetamine and cocaine abusers. J. Addict. Dis. 21, 61–74.

Sindicich, N., Stafford, J., Burns, L., 2009. An overview of the 2009 EDRS: the regular ecstasy user survey findings. EDRS Drug Trends Bull. December 2009, National Drug and Alcohol Research Centre, University of New South Wales.

Soria, G., Mendizábal, V., Touriño, C., Robledo, P., Ledent, C., Parmentier, M., et al., 2005. Lack of CB1 cannabinoid receptor impairs cocaine self-administration. Neuropsychopharmacology 30 (9), 1670–1680.

Spano, M.S., Fattore, L., Cossu, G., Deiana, S., Fadda, P., Fratta, W., 2004. CB1 receptor agonist and heroin, but not cocaine, reinstate cannabinoid-seeking behaviour in the rat. Br. J. Pharmacol. 143 (3), 343–350.

Spano, M.S., Fadda, P., Fratta, W., Fattore, L., 2010. Cannabinoid-opioid interactions in drug discrimination and self-administration: effect of maternal, postnatal, adolescent and adult exposure to the drugs. Curr. Drug Targets 11 (4), 450–461.

Stephens, R.S., Roffman, R.A., Simpson, E.E., 1994. Treating adult marijuana dependence: a test of the relapse prevention model. J. Consult. Clin. Psychol. 62, 92–99.

Tanda, G., 2007. Modulation of the endocannabinoid system: therapeutic potential against cocaine dependence. Pharmacol. Res. 56 (5), 406–417.

Tanda, G., Munzar, P., Goldberg, S.R., 2000. Self-administration behavior is maintained by the psychoactive ingredient of marijuana in squirrel monkeys. Nat. Neurosci. 3 (11), 1073–1074.

Teichtahl, H., Wang, D., Cunnington, D., Kronborg, I., Goodman, C., Prodromidis, A., et al., 2004. Cardiorespiratory function in stable methadone maintenance treatment (MMT) patients. Addict. Biol. 9 (3–4), 247–253.

Thanos, P.K., Dimitrakakis, E.S., Rice, O., Gifford, A., Volkow, N.D., 2005. Ethanol self-administration and ethanol conditioned place preference are reduced in mice lacking cannabinoid CB1 receptors. Behav. Brain Res. 164 (2), 206–213.

Thiemann, G., van der Stelt, M., Petrosino, S., Molleman, A., Di Marzo, V., Hasenöhrl, R.U., 2008. The role of the CB1 cannabinoid receptor and its endogenous ligands, anandamide and 2-arachidonoylglycerol, in amphetamine-induced behavioural sensitization. Behav. Brain Res. 187 (2), 289–296.

Touriño, C., Ledent, C., Maldonado, R., Valverde, O., 2008. CB1 cannabinoid receptor modulates 3,4-methylenedioxymethamphetamine acute responses and reinforcement. Biol. Psychiatry 63 (11), 1030–1038.

Tyndale, R.F., Payne, J.I., Gerber, A.L., Sipe, J.C., 2007. The fatty acid amide hydrolase C385A (P129T) missense variant in cannabis users: studies of drug use and dependence in Caucasians. Am. J. Med. Genet. B Neuropsychiatr. Genet. 144B (5), 660–666.

UNODC, World Drug Report, 2013. United Nations publication, Sales No. E.13.XI.6.

Valjent, E., Mitchell, J.M., Besson, M.J., Caboche, J., Maldonado, R., 2002. Behavioural and biochemical evidence for interactions between delta 9-tetrahydrocannabinol and nicotine. Br. J. Pharmacol. 135, 564–578.

Vaughn, L.K., Mantsch, J.R., Vranjkovic, O., Stroh, G., Lacourt, M., Kreutter, M., et al., 2012. Cannabinoid receptor involvement in stress-induced cocaine reinstatement: potential interaction with noradrenergic pathways. Neuroscience 204, 117–124.

Viganò, D., Cascio, M.G., Rubino, T., Fezza, F., Vaccani, A., Di Marzo, V., et al., 2003. Chronic morphine modulates the contents of the endocannabinoid, 2-arachidonoyl glycerol, in rat brain. Neuropsychopharmacology 28 (6), 1160–1167.

Vinod, K.Y., Hungund, B.L., 2005. Endocannabinoid lipids and mediated system: implications for alcoholism and neuropsychiatric disorders. Life Sci. 77 (14), 1569–1583.

Vinod, K.Y., Hungund, B.L., 2006. Role of the endocannabinoid system in depression and suicide. Trends Pharmacol. Sci. 27 (10), 539–545.

Vinod, K.Y., Sanguino, E., Yalamanchili, R., Manzanares, J., Hungund, B.L., 2008. Manipulation of fatty acid amide hydrolase functional activity alters sensitivity and dependence to ethanol. J. Neurochem. 104 (1), 233–243.

Vinod, K.Y., Kassir, S.A., Hungund, B.L., Cooper, T.B., Mann, J.J., Arango, V., 2010. Selective alterations of the CB1 receptors and the fatty acid amide hydrolase in the ventral striatum of alcoholics and suicides. J. Psychiatr. Res. 44 (9), 591–597.

Viveros, M.P., Marco, E.M., File, S.E., 2006. Nicotine and cannabinoids: parallels, contrasts and interactions. Neurosci. Biobehav. Rev. 30 (8), 1161–1181.

Vlachou, S., Panagis, G., 2014. Regulation of brain reward by the endocannabinoid system: a critical review of behavioral studies in animals. Curr. Pharm. Des. 20 (13), 2072–2088.

Voytek, B., Berman, S.M., Hassid, B.D., Simon, S.L., Mandelkern, M.A., Brody, A.L., et al., 2005. Differences in regional brain metabolism associated with marijuana abuse in methamphetamine abusers. Synapse 57, 113–115.

Wachtel, S.R., de Wit, H., 2000. Naltrexone does not block the subjective effects of oral delta9-THC in humans. Drug Alcohol Depend. 59, 251–260.

Wang, L., Liu, J., Harvey-White, J., Zimmer, A., Kunos, G., 2003. Endocannabinoid signaling via cannabinoid receptor 1 is involved in ethanol preference and its age-dependent decline in mice. Proc. Natl Acad. Sci. USA 100 (3), 1393–1398.

Weizman, T., Gelkopf, M., Melamed, Y., Adelson, M., Bleich, A., 2004. Cannabis abuse is not a risk factor for treatment outcome in methadone maintenance treatment: a 1-year prospective study in an Israeli clinic. Aust. NZ J. Psychiatry 38 (1–2), 42–46.

Xi, Z.X., Peng, X.Q., Li, X., Song, R., Zhang, H.Y., Liu, Q.R., et al., 2011. Brain cannabinoid CB_2 receptors modulate cocaine's actions in mice. Nat. Neurosci. 14 (9), 1160–1166.

Zhang, Q.Y., Zhang, M., Cao, Y., 2012. Exposure to morphine affects the expression of endocannabinoid receptors and immune functions. J. Neuroimmunol. 247 (1–2), 52–58.

Zuo, L., Kranzler, H.R., Luo, X., Yang, B.Z., Weiss, R., Brady, K., et al., 2009. Interaction between two independent CNR1 variants increases risk for cocaine dependence in European Americans: a replication study in family-based sample and population-based sample. Neuropsychopharmacology 34 (6), 1504–1513.