Chapter 74

Cannabis and the Mesolimbic System

Carla Cannizzaro[1], Marco Diana[2]

[1]Department of Sciences for Health Promotion and Maternal Care, School of Medicine, University of Palermo, Palermo, Italy; [2]Department of Drug Sciences, School of Pharmacy, University of Sassari, Sassari, Italy

Abbreviations

CB1 Cannabinoid 1 subtype
CBD Cannabidiol
CPP Conditioned place preference
DA Dopamine
DSE Depolarization-induced suppression of excitation
DSI Depolarization-induced suppression of inhibition
ICSS Intracranial self-stimulation
LTD Long-term depression
LTP Long-term potentiation
mPFC Medial prefrontal cortex
MSN Medium spiny neurons
Nacc Nucleus accumbens
RMTg Rostromedial tegmental nucleus
VS Ventral striatum
VTA Ventral tegmental area
Δ^9-THC Δ^9-Tetrahydrocannabinol

THE DOPAMINERGIC MESOLIMBIC SYSTEM

Various classes of chemicals, including nitrogenous compounds, amino acids, hydrocarbons, sugar, terpenes, and simple fatty acids, together contribute to the unique pharmacological and toxicological properties of cannabis (Svizenska, Dubovy, & Sulcova, 2008). Among them Δ^9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol, the two main ingredients of the *Cannabis sativa* plant, have distinct symptomatic and behavioral effects (Iversen, 2003). Δ^9-THC is the primary psychoactive constituent and is believed to be primarily responsible for the resulting cognitive effects, psychotic symptoms, and anxiety, as well as the addictive potential, of smoked cannabis (Leweke & Koethe, 2008). Although many factors contribute to addiction, cannabis and other drugs of abuse act upon the mesolimbic reward circuitry in the mammalian brain, thus promoting repetition of drug taking, a necessary precondition for the neuronal adaptations that underlie addiction. Indeed dopamine (DA) in the mesocorticolimbic system has long been considered essential for translating motivations into goal-directed actions. The reinforcing effects of major classes of abused drugs are produced through actions in the mesolimbic system, which originates from A10 DAergic neurons in the ventral tegmental area (VTA) and innervates the limbic component of the basal ganglia, to influence motivational, emotional, contextual, and affective components of behavior (Ikemoto, Qin, & Liu, 2005). Drug self-administration and electrical self-stimulation studies have shown that DAergic projections from the VTA are crucial in reward but DA is not a sole mediator. Major glutamatergic projections are provided by the amygdala, hippocampus, and medial prefrontal cortex (mPFC) to the nucleus accumbens (Nacc), which consists of anatomically heterogeneous elements classically represented by the core and shell. The Nacc has two main outputs, which are γ-aminobutyric acid (GABA)-ergic projections to the ventral pallidum (so-called indirect pathway) and the VTA/substantia nigra pars reticulata (direct pathway). Both the ventral pallidum and the VTA send GABAergic efferents to the medial dorsal thalamus. Glutamatergic projections from the medial dorsal thalamus to the mPFC close this circuitry (Figure 1). Studies suggested that within the Nacc shell, the medial portion is more responsive to psychomotor stimulants than its lateral counterpart; moreover, the medial shell, but not the core, supports self-administration of Δ^9-THC. Anatomically correlated, the medial olfactory tubercle and medial Nacc shell form the medial portion of the ventral striatum (VS), which appears to be more responsive to the rewarding effects of DAergic drugs than its lateral counterparts. Indeed DA neurons projecting to the medial VS are localized posteromedially in the VTA in relation to those projecting to the lateral VS, indicating that the medial part of the VTA–VS DA system is particularly important for reward and arousal and that the lateral portion is more closely involved in specific conditioned responses (Ikemoto et al., 2005). In 2009, a new nucleus was identified and named the rostromedial tegmental nucleus (RMTg) (Jhou, Fields, Baxter, Saper, & Holland, 2009), located close to the VTA so that the posterior end of the VTA overlaps with the anterior part of the RMTg. It contains predominantly GABAergic neurons, whose major projections target DAergic neurons in the VTA and substantia nigra. Together with the lateral habenula, the RMTg may represent a site of tonic inhibition over VTA DAergic neurons and may be a key site through which deprivation-type signals are conveyed over access-type messages in the mesolimbic system. One of the hallmarks of abused drugs is the ability to increase DA signaling from VTA neurons (Di Chiara & Imperato, 1988). These well-characterized cells fire in two distinct modes: low-frequency (1–5 Hz) tonic activity, which produces a steady DAergic "tone" on high-affinity inhibitory D2-like DA receptors of the mesolimbic system, and high-frequency (>20 Hz within bursts) phasic activity, which results in increased synaptic DA content

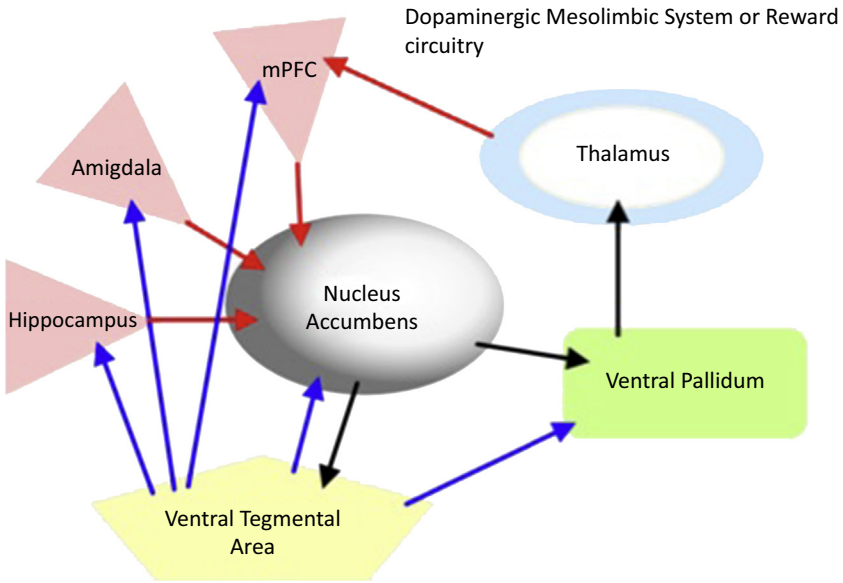

FIGURE 1 Schematic illustration of the mesolimbic system. Red arrows indicate glutamatergic pathways; black arrows indicate GABAergic pathways; blue arrows indicate DAergic pathways. See text for additional details. *Modified from Piercea and Kumaresana (2006).*

sufficient to occupy low-affinity D1-like receptors. The baseline DAergic tone is believed to facilitate long-term depression (LTD) at corticostriatal synapses and suppress activity of the indirect pathway of the basal ganglia (Shen, Flajolet, Greengard, & Surmeier, 2008); on the other hand D1 receptor activation following reward-related stimuli is coupled to an enhancement in long-term potentiation (LTP) of the excitatory transmission and to the activation of the striatal direct pathway, thereby motivating behavior (Grace, Floresco, Goto, & Lodge, 2007). Stimuli promoting burst activity of DAergic neurons in the VTA also produce transient increases in extracellular DA concentration at the terminal fields of the mesolimbic system, such as the Nacc (Diana, 1998). A shift in midbrain DAergic neuron activation from tonic low-frequency to phasic high-frequency firing results from changes in synaptic input from glutamate and GABA afferents to VTA DAergic cells. Indeed excitatory glutamatergic afferents project from sensory and cognitive regions, including the prefrontal cortex and the extended amygdala, whereas GABAergic input comes from the basal ganglia and the RMTg. Thus, to activate the "conditional" burst firing of DAergic neurons, glutamatergic input must activate *N*-methyl-D-aspartate (NMDA) glutamate receptors localized at synapses impinging on midbrain DA neurons (Overton & Clark, 1997). Conversely GABAergic input to the same cells dampens burst firing and returns the neurons to baseline pacemaker-like activity. Notably, the maintenance of midbrain DAergic firing patterns requires a balance between excitatory and inhibitory VTA afferent signals, and a key role in the "governance" of these modulatory networks is strategically played by the endocannabinoid system.

CANNABINOIDS IN THE REWARD CIRCUITRY

Although the euphorigenic properties of cannabis preparations have been appreciated by humans for centuries, only lately have we acquired the experimental tools to evaluate cannabinoid reward and abuse liability in experimental animals. Historically, intracranial self-stimulation (ICSS) has been utilized in rodents to study how pharmacological or molecular manipulations affect brain reward function: ICSS is an operant behavioral paradigm in which animals would work to obtain intracranial stimulation through electrodes implanted into discrete brain areas (such as the mesolimbic brain reward areas). The conditioned place preference (CPP) paradigm is based on the assumption that animals learn to approach stimuli paired with rewards and to avoid stimuli paired with aversive agents. In this procedure, the animal develops an association between the subjective state produced by the drug (e.g., a heightened feeling of euphoria comparable to pleasure in humans) and the environmental cues present during the drug state. Intravenous drug self-administration has been one of the most direct approaches to studying the rewarding properties of drugs of abuse in experimental animals, such as rodents or primates. In this behavioral paradigm, based on operant conditioning, animals learn to make an operant response, such as pressing a lever in an operant chamber or inserting their nose into a hole, to self-administer a reinforcer (e.g., a drug of abuse) after the completion of the reinforcement schedule requirement. The rewarding properties of Δ^9-THC are clearly shown by a decrease in brain-stimulation reward thresholds and an increase in self-administration behavior and CPP in a dose-dependent manner. It is now clear that cannabinoids exert emotional and motivational effects and produce drug reinforcement/drug-seeking behavior. To characterize the actions of cannabinoids on reward circuitry, the ability of Δ^9-THC to modulate DA transmission in the mesolimbic system has been largely investigated. Cannabinoid systemic administration enhances extracellular DA concentration in the Nacc shell, by increasing both the baseline firing rates and the bursting frequency of midbrain DAergic neurons. Smoked marijuana produces subjective feelings of well-being and euphoria in humans that are inhibited by the concomitant administration of rimonabant, a cannabinoid 1 subtype (CB1) receptor antagonist/inverse agonist; similarly DA enhancement in the Nacc, together with the related phenotypes, is

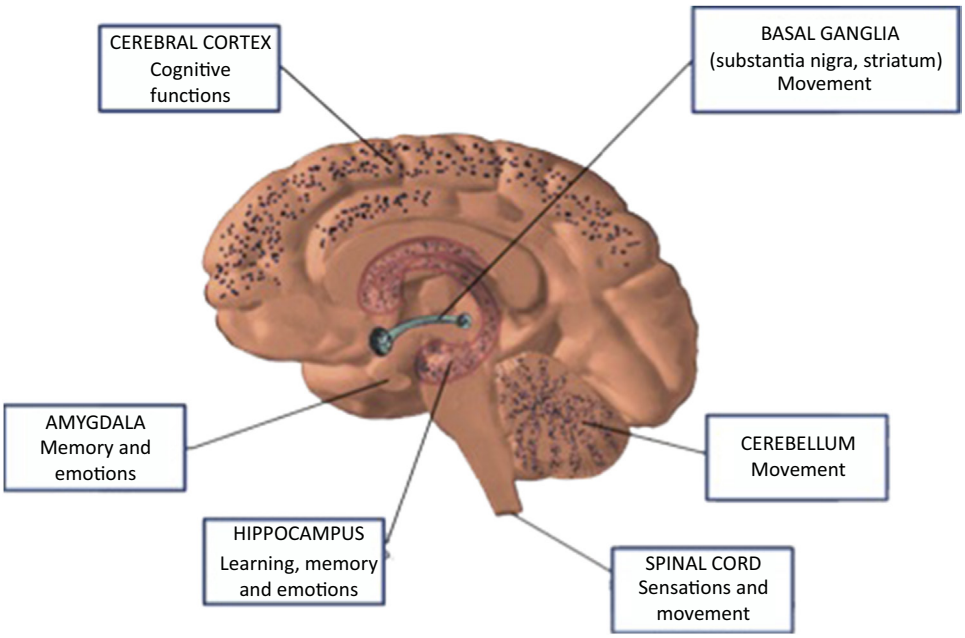

FIGURE 2 CB1 receptor distribution in the brain: correlation with functions that are affected by cannabinoid activity. *From Serpelloni, Diana, Gomma, and Rimondo (2011).*

abolished by blocking the same receptors, suggesting that many, if not all, psychological and neurochemical effects of cannabis in the mesolimbic system depend on the activation of CB1 receptors (Figure 2). Interestingly, while VTA DAergic cells release endocannabinoids during phasic activation, they do not express CB1 receptors. This suggests that cannabinoids can produce an enhancement in DA release in the mesolimbic system from VTA neurons via an indirect mechanism: indeed the midbrain contains GABAergic neurons that modulate DAergic cell activity, through $GABA_A$ receptors on DA somata (Riegel & Lupica, 2004). The prior application of the $GABA_A$ receptor antagonist bicuculline to VTA-containing slices blocked the excitatory effect exerted by cannabinoids on DA release. In other words, cannabinoids can enhance DA transmission through the inhibition of the inhibitory GABAergic tone, thus disinhibiting the VTA DAergic neurons to discharge. In line with this evidence Lupica and Riegel (2005) proposed a model of reciprocal interaction between DA and endocannabinoids in the mesolimbic system. Indeed, endocannabinoids released as a consequence of enhanced activation of VTA neurons upon depolarization act as "retrograde messengers," activate presynaptic CB1 receptors, and inhibit GABA release from the terminals (Figure 3). The majority of the evidence suggests that 2-arachidonoylglycerol mediates most forms of CB1-mediated retrograde regulation of synaptic transmission, i.e., depolarization-induced suppression of inhibition or excitation. Much more interactions occur, however, between DA and cannabinoids in the mesolimbic system, and it is noteworthy that the direct infusion of Δ^9-THC into the VTA does not increase DA accumulation in the Nacc. CB1 receptors are also located on GABAergic terminals originating from Nacc medium spiny output neurons that target $GABA_B$ receptors on DA neurons in the VTA, suggesting a second possible mechanism of disinhibition (Heimer, Zahm, Churchill, Kalivas, & Wohltmann, 1991). Thus, cannabinoids acting at CB1 receptors can control the release of GABA in the VTA that is derived from both intrinsic and extrinsic sources, indicating that the inputs from the Nacc to the VTA may represent a critical pathway for the expression of cannabinoid-induced reward in the mesolimbic system. Synthetic cannabinoid agonists and endocannabinoids, acting as retrograde messengers, can also inhibit glutamate release onto neurons in the mesolimbic circuitry and in the VTA in particular (Melis et al., 2004). This puzzle is made more complicated by the finding that glutamate release onto Nacc medium spiny neurons (MSNs) is also inhibited by cannabinoid agonists, apparently as a result of the activation of CB1 receptors coupled to voltage-dependent Kþ channels in the glutamatergic nerve terminals. The reduction of glutamatergic inputs that arise from neurons in the prefrontal cortex to the Nacc by CB1 receptor activation would reduce the excitation of GABAergic Nacc MSNs projecting to DA neurons in the VTA, and thereby would decrease the inhibition of DA neurons. Again, the relative contribution of the CB1 receptor modulation of GABAergic and glutamatergic synaptic transmission to the output of the Nacc might rely upon the functional setting under which each system transmits. The activation of CB1 receptors by endocannabinoids can modify the strength of LTP and can also initiate long-term forms of synaptic plasticity, including LTD (Kortleven, Fasano, Thibault, Lacaille, & Trudeau, 2011), in the mesolimbic system. Indeed, CB1-mediated long-term reduction of transmitter release at the same synapse defines endocannabinoid LTD, which emerged for the first time in 2002 at excitatory synapses in dorsal striatum. Since then, endocannabinoid LTD has been reported in several other brain structures such as the Nacc, amygdala and hippocampus, somatosensory cortex, prefrontal cortex, and VTA. Endocannabinoids and functional CB1 receptors are required to observe the LTD of glutamatergic cortical synaptic inputs to striatal MSNs; contextually, presynaptic activity is required in terms of presynaptic NMDA receptor recruitment. Endocannabinoid LTD is a widely expressed phenomenon in the brain that can be observed also

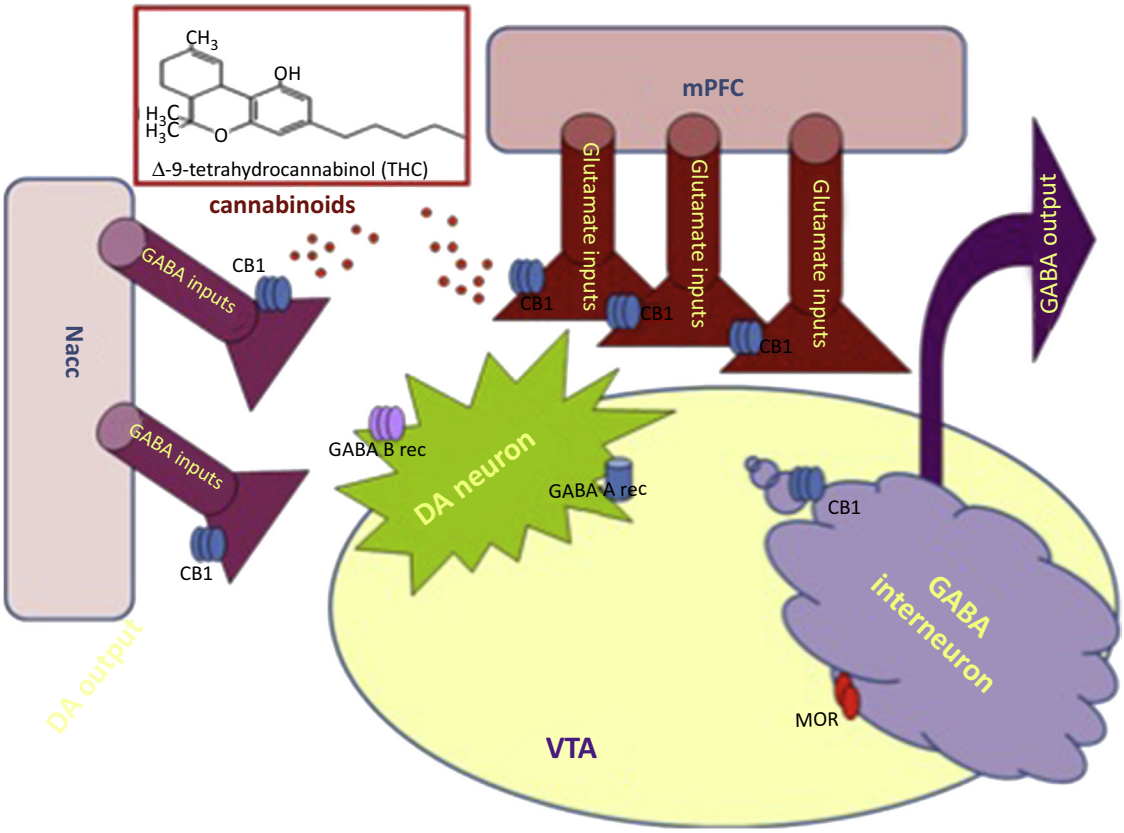

FIGURE 3 Cellular elements mediating cannabinoid actions in the mesolimbic system, through activation of presynaptic CB1 receptors. Note the extrinsic and intrinsic GABAergic inputs to the VTA. MOR, μ opioid receptor; DA, dopamine; Nacc, nucleus accumbens. *Modified from Lupica, Riegel, and Hoffman (2004).*

in inhibitory synapses. Although the precise role that LTD plays in regulating the function of the dorsal and ventral striatum is not known as of this writing, it has been speculated that the long-term changes in synaptic efficacy mediated by this system may be involved in communicating enduring information as to reward salience and in the establishment of motor habits associated with compulsive drug use, too (Gerdeman & Lovinger, 2003). CB1 receptors are located on both GABAergic and glutamatergic axon terminals in the Nacc, where they inhibit the release of each of these neurotransmitters. However, following in vivo treatment with Δ^9-THC for 1 week, the inhibition of glutamatergic and GABAergic synaptic transmission by WIN 55,212-2, a potent cannabinoid agonist, is greatly diminished, confirming CB1 receptor tolerance (Hoffman, Riegel, & Lupica, 2003). Synaptic remodeling of mesolimbic circuitries by long-term plasticity may represent a mechanism through which drug use may progress from casual to impulsive. Notably, short- or long-term exposure to Δ^9-THC can limit the degree to which Nacc glutamate synapses undergo LTD, and this appears to result from a downregulation of CB1 receptor function and the ability of cannabinoids to initiate this form of synaptic plasticity (Hoffman et al., 2003). Such a phenomenon amounts to metaplasticity, which refers to enduring changes in the ability of neurons to generate synaptic plasticity (Abraham, 2008). Considerable evidence using behavioral genetic approaches has demonstrated several important functional interrelationships between cannabinoids and opiate-related reward processing, both in terms of opiate-related reward behaviors and in terms of CB1 receptor-mediated modulation of neural regions critical for opiate reward processing, such as the mesocorticolimbic system. The mammalian VTA is a critical neural substrate for the processing of the primary rewarding properties of opiates, through DA-dependent and non-DA neuronal substrates (Laviolette, Gallegos, Henriksen, & van der Kooy, 2004; Nader & Van der Kooy, 1997), and a large body of evidence has demonstrated that cannabinoid compounds can acutely activate both the opiate and the DAergic signaling systems. For example, the acute administration of Δ^9-THC has been reported to increase levels of β-endorphins and enkephalinergic peptides directly in the mesolimbic DA pathway, including the VTA and Nacc. As a consequence, cannabinoids would alter motivational processes mediated by the Nacc and also play a role in modulating the reinforcing properties of other abused drugs, ultimately making long-term changes to neural circuitries and behavior.

CANNABIS DEPENDENCE

The effects sought by cannabis users seem to be produced primarily by Δ^9-THC in a dose-related manner so that a higher THC content leads to an increase in the subjective effects of this drug, probably enhancing the risk of dependence and psychotic symptoms of cannabis users (Hall & Degenhardt, 2009). Indeed compelling evidence suggests that exposure to marijuana during

critical, adolescent windows of neurodevelopment is positively correlated with an increased propensity to develop schizophrenia-related psychoses in early adulthood. Functional interactions between cannabinoid signaling and mesolimbic DAergic transmission stand as a nexus point to understanding how dysregulation of the endocannabinoid system may relate to the well-established aberrations in DAergic transmission, as a core neuropathological feature of both addiction and schizophrenia (Tan, Ahmad, Loureiro, Zunder, & Laviolette, 2014). In epidemiological studies about 9% of those who ever use this drug become daily users, rising to 16% when the consumption is initiated during adolescence; heavy or "regular" cannabis use is usually defined as daily or near-daily use of up to three to five joints of potent cannabis a day. This pattern of consumption, when continued over years and decades, predicts increased risk of many of the adverse health effects attributed to cannabis. Both tolerance and dependence can develop with chronic use, as well as withdrawal signs and symptoms, as reported below (Diana, Melis, Muntoni, & Gessa, 1998; Fattore, Fadda, Spano, Pistis, & Fratta, 2008). In 1993 the first definition of cannabis dependence in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), third edition, included impaired control over cannabis use and difficulty ceasing use despite harms caused by it. In many countries such as Australia, Canada, and the United States, cannabis dependence is the most commonly treated type of drug dependence after alcohol and tobacco. This is not to be attributed to an increase in the number of people smoking marijuana, but to the greater potency of the marijuana that individuals are exposed to. Indeed, the average potency of Δ^9-THC in seized marijuana has increased from 3% in 1992 to 13.2% in 2012, and some samples of marijuana analyzed displayed a Δ^9-THC content of more than 30% (UNODC, 2014). Despite the common belief that cannabis preparations do not produce withdrawal, clinical reports on chronic consumers of even low daily doses of cannabis derivatives described the onset of physical dependence, defined by a withdrawal response that occurs upon cessation of drug administration. Abstinence from marijuana smoke or oral Δ^9-THC produces indeed symptoms such as irritability, anger, anxiety, decreased appetite, weight loss, restlessness, craving, and disrupted sleep. These symptoms usually occur 24 h after last use, peak in 2–3 days, and last about 2–3 weeks (Budney & Hughes, 2006). Approximately 60–90% of individuals experiencing withdrawal during abstinence use marijuana to alleviate the symptoms, indicating that Δ^9-THC plays an essential role in the development of dependence and in the expression of withdrawal. Dependence and withdrawal can be induced and precipitated, respectively, in the animal model (Diana et al., 1998). Behavioral signs observed during precipitated withdrawal include whirling, wet-dog shakes, sniffing, front-paw tremor, genital licking, erection, ataxia, diarrhea, mastication, and piloerection (Diana et al., 1998; Wilson, Varvel, Harloe, Martin, & Lichtman, 2006). Because withdrawal is precipitated by a CB1 antagonist and alleviated by Δ^9-THC, it is clear that cannabinoid dependence is largely mediated by CB1 receptors in rodents. Disturbances in cannabinoid transmission within the mesocorticolimbic pathway may underlie DAergic dysregulation linked to a variety of neuropsychiatric disorders such as addiction and schizophrenia. Within the prefrontal cortex, CB1 receptor transmission appears to control emotional salience, in the context of both aversive, negative events and rewarding, appetitive, motivational stimuli. The underlying mechanisms are still to be elucidated. Moreover, cannabis use is associated with impairments in cognitive functions, including learning and memory, attention, and decision-making. Clinical findings have demonstrated significantly diminished DA synthesis capacity in regular marijuana users compared with nonusers and evidence of attenuated DA receptor expression levels in current or recently abstinent marijuana users (Bloomfield et al., 2014; Urban et al., 2012). In humans some studies have shown volume reductions in the hippocampus, amygdala, and cerebellum; greater gray matter density in marijuana users than in control participants in the left Nacc extending to the subcallosal cortex, hypothalamus, sublenticular extended amygdala, and left amygdala; volume increase in the left Nacc; and significant shape differences in the left Nacc and right amygdala. These observations suggest that marijuana exposure, even in young recreational users, is associated with exposure-dependent alterations of the neural matrix of core reward structures that are consistent with animal evidence of changes in dendritic arborization in the mesolimbic system (Gilman et al., 2014). The appearance of overt abstinence signs upon cessation of drug administration is paralleled by structural and functional neuroimaging studies on cannabis use (Budney & Hughes, 2006; Iversen, 2003). Moreover, work has shown that withdrawal from a regimen of chronic cannabinoid administration profoundly affects the mesolimbic system, causing a shrinkage of DA neurons in the VTA and a reduction in the spine density of dendrites of MSNs of the Nacc shell (Spiga, Lintas, Migliore, & Diana, 2010; Spiga et al., 2014; Figure 4); this represents a morphological correlate of the functional deficits detected by electrophysiological and neurochemical means that ultimately may contribute to the negative emotional state that characterizes withdrawal (Koob & Le Moal, 2001). In this regard, the spines' loss, in addition to contributing to the reduction in the already abated DA transmission, could explain the downregulation of CB1 receptors after Δ^9-THC withdrawal as well as the CB1-mediated inhibition of excitatory synaptic transmission between the prefrontal cortex and the Nacc. These findings suggest that cannabis affecting dendritic spines provides another example of drug-induced aberrant neural plasticity with marked reflections on the physiology of synapses, system structural organization, and neuronal circuitry remodeling that promote the transition from chronic drug intake to "addiction."

APPLICATIONS TO OTHER ADDICTIONS AND SUBSTANCE MISUSE

In this chapter we have approached the topic describing cannabis activity in the mesolimbic system. Cannabis is able, through its principal active ingredient Δ^9-THC, to increase DA release in the mesolimbic system, paralleling the activity of most abused drugs. Nevertheless, beyond this fact, exogenous and endogenous cannabinoids can alter synaptic process in both the Nacc and the VTA, suggesting that the regulation of inner and outer neural circuits to the mesolimbic system is relevant if not essential for the expression of value-attribution processing and in the modulation of reward-seeking behavior for different drugs of abuse. Chronic use of cannabis can therefore exert a continued regulation of these processes, thus contributing to addiction to several classes of drugs, such as alcohol. In particular, CB1 receptor manipulation is reported to affect

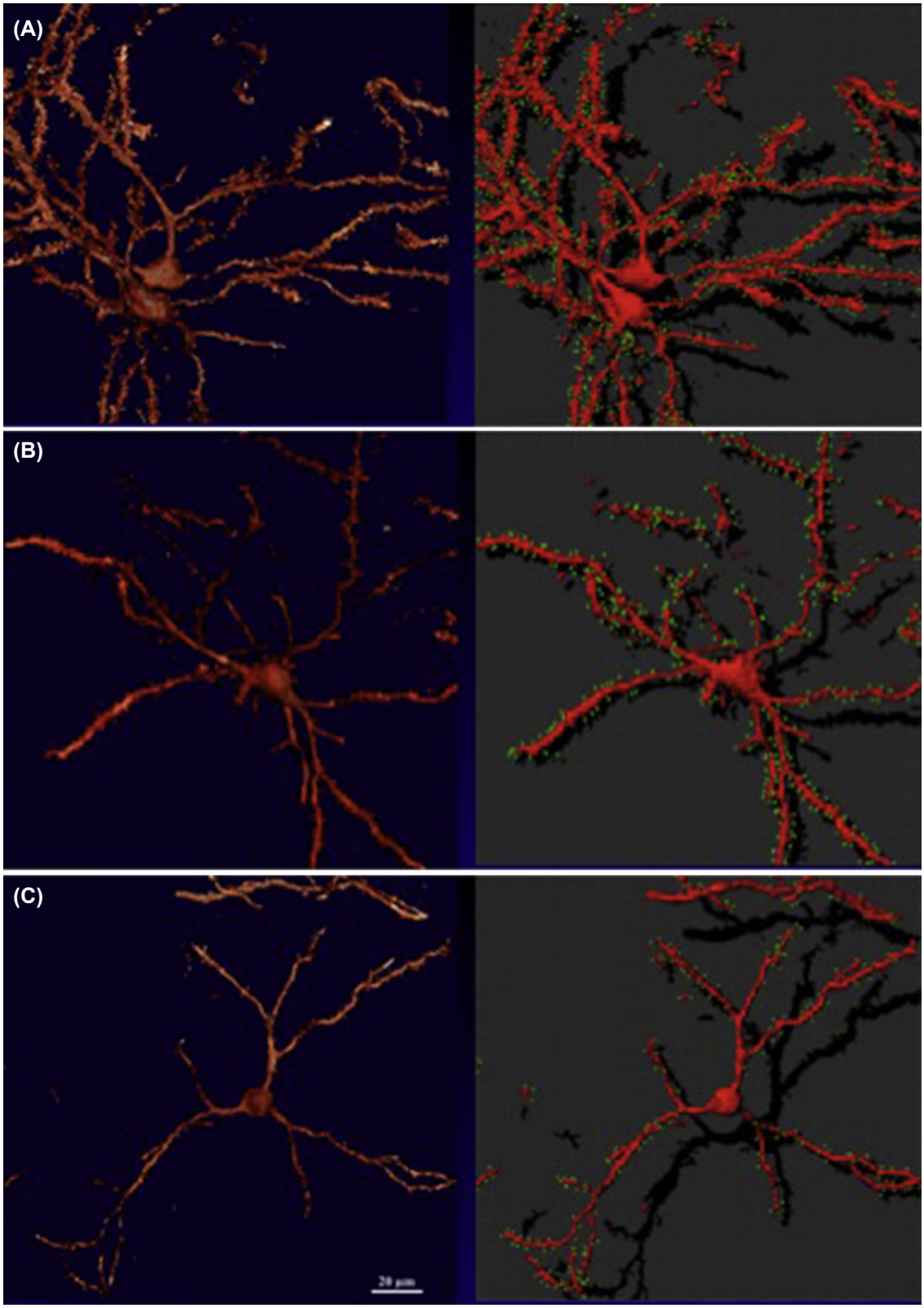

FIGURE 4 Representative confocal reconstructions synthesizing major findings on Golgi–Cox-stained MSNs in the Nacc. (A) MSNs from the core control group, (B) MSN from the shell control group, and (C) MSN from the shell in the Δ^9-THC-treated group. *From Spiga et al. (2010).*

ethanol-related behavior, and in fact CB1 antagonism decreases both voluntary ethanol intake and relapse to ethanol in several experimental models. Consistently, publications have shown that administration of a pure antagonist at the CB1 receptor, such as AM281, is able to reduce the motivational properties of the neuroactive metabolite of alcohol, acetaldehyde, in an operant-conflict self-administration paradigm. In particular, the administration of AM281 decreases drug seeking when the drug is not available, drug taking after a period of forced abstinence, and drug-related compulsive behavior, in an experimental model of drug use despite negative consequences (Plescia et al., 2014). The manipulation of the endocannabinoid system might represent a useful therapeutic strategy to treat addiction-related behaviors.

DEFINITION OF TERMS

Cannabis *C. sativa* L. (hemp) is an annual flowering plant that gives origin to marijuana, from dried leaves and female flowering tops, and hashish, from the resin, which originates on these female flowering tops.

Δ^9-Tetrahydrocannabinol Δ^9-THC is the main psychoactive component of *Cannabis* that was first isolated in 1964. It binds to G-protein-coupled cannabinoid receptors in the nervous system and in the periphery.

CB1 receptors These receptors are the most abundant G-protein-coupled receptors in the brain: they are highly expressed in the basal ganglia nuclei in the hippocampus, cerebellum, and neocortex. They modulate neurotransmitter release.

Retrograde messenger It is a signaling molecule that is produced by the postsynaptic terminal, travels "backward" across the synaptic cleft, and binds to the presynaptic membrane where it exerts its main physiological function.

Depolarization-induced suppression of inhibition or excitation These are short-term forms of synaptic plasticity induced by CB1 activation, which result in prevention of transmitter release through the inhibition of voltage-gated Ca^{2+} channels and/or increase in K^+ conductance.

Reward system The reward circuitry of the brain consists of subcortical nuclei that are synaptically interconnected. It classically consists of the VTA and the Nacc, which play key roles in the processing of rewarding environmental stimuli and in the setup of addictive behaviors.

Reinforcers Reinforcers refers to those stimuli—substances or acts—that are able to activate the DAergic mesolimbic system and produce a sense of euphoria and well-being, thus increasing the probability of repeating the behaviors paired with them.

Dependence This is a form of receptor and postreceptor plasticity, which establishes as a physiological response to repeated doses of many medications, including opioids, antidepressants, and β-blockers, and which is followed by a withdrawal syndrome upon abrupt cessation of administration.

Cannabis addiction It occurs with heavy chronic use in individuals who report difficulties in controlling their use and who continue cannabis consumption despite the personal experience of adverse consequences.

Cannabis use disorder This is the term that the DSM-5 work group has recommended to subsume cannabis abuse/dependence, indicating the main clinical criteria for the diagnosis.

KEY FACTS OF THE "ADDICTIVE" SPINES IN THE NUCLEUS ACCUMBENS

- Dendritic spines are the main postsynaptic compartments of excitatory synapses in the brain with peculiar and distinctive morphological features consisting of a bulbous head and a thinner neck that connects the spine to the dendritic shaft.
- At the ultrastructural level, the spine head is characterized by an electron-dense matrix of receptors and supporting proteins collectively known as the postsynaptic density, which dynamically changes its structure and composition during development and in response to synaptic activity.
- A significant subpopulation of spines on the distal dendrites of the MSNs in the Nacc possesses a particular synaptic architecture, called "striatal microcircuit" or "synaptic triad," that involves both DAergic and glutamatergic axons.
- All addictive drugs commonly abused by humans evoke variations on DA concentrations within the Nacc and this may have a role in spine density, morphology, and synaptic strength in the entire neuronal mesolimbic pathway.
- The withdrawal syndrome after chronic drug administration seems to be a crucial point of the addictive process that is manifested by the induction of rapid changes in dendritic spine density and morphology.
- Confocal analysis of Golgi–Cox-stained MSNs of the Nacc revealed a decrease in spine density in the shell during morphine, alcohol, and cannabis withdrawal, while no changes in the number of spines were observed during chronic treatments.
- As long as the drug is "on-board" it supports spine persistence and function, whereas abrupt withdrawal discloses spine pruning and synaptic dysfunction.
- Withdrawal after chronic drug intake induces major changes at the neural level, which, in turn, will elicit behavioral changes, thus representing the "driving force" in the transition from chronic drug intake to addiction.

SUMMARY POINTS

- This chapter focuses on cannabis, the most widely produced and most frequently used illegal plant-based drug in Europe, whose main active ingredient, Δ^9-THC, is able to heavily affect the mesolimbic reward circuitry.
- The regional distribution of CB1 receptors corresponds to the behavioral effects of cannabinoids, including those on mood, motor coordination, autonomic function, memory, sensation, and cognition.
- Cannabis as much as other drugs of abuse functions as a reinforcer in the brain through its actions on the mesolimbic system, where it produces an increase in the release of DA.
- In the mesolimbic system, the medial portions of the VS and the VTA appear to be more responsive to the rewarding effects of DAergic drugs than their lateral counterparts.
- Actions of cannabis derivatives on DA transmission are mediated by the modulation of GABA and glutamate release.
- Cannabis-induced subjective feelings of well-being and euphoria in humans are inhibited by the concomitant administration of CB1 receptor antagonists, suggesting that many, if not all, psychological and neurochemical effects of cannabis in the mesolimbic system depend on the activation of CB1 receptors.

- Chronic consumers of even low daily doses of cannabis derivatives display, upon cessation of drug administration, the appearance of overt abstinence signs paralleled by structural anomalies related to cannabis use.
- Withdrawal from a regimen of chronic cannabinoid administration profoundly affects the mesolimbic system, causing a shrinkage of DA neurons in the VTA, a reduction in spine density of the Nacc shell, and overall reduction in DA transmission that ultimately may contribute to the negative emotional state that characterizes withdrawal.

ACKNOWLEDGMENT

A special acknowledgment goes to Miss Carlotta Vita for her much appreciated graphic support.

REFERENCES

Abraham, W. C. (2008). Metaplasticity: tuning synapses and networks for plasticity. *Nature Reviews Neuroscience*, *9*(5), 387.

Bloomfield, M. A., Morgan, C. J., Egerton, A., Kapur, S., Curran, H. V., & Howes, O. D. (2014). Dopaminergic function in cannabis users and its relationship to cannabis- induced psychotic symptoms. *Biological Psychiatry*, *75*, 470–478.

Budney, A. J., & Hughes, J. R. (2006). The cannabis withdrawal syndrome. *Current Opinion in Psychiatry*, *19*, 233–238.

Di Chiara, G., & Imperato, A. (1988). Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proceedings of the National Academy of Sciences of the United States of America*, *85*, 5274–5278.

Diana, M. (1998). Drugs of abuse and dopamine cell activity. *Advances in Pharmacology*, *42*, 998–1001.

Diana, M., Melis, M., Muntoni, A. L., & Gessa, G. L. (August 18, 1998). Mesolimbic dopaminergic decline after cannabinoid withdrawal. *Proceedings of the National Academy of Sciences of the United States of America*, *95*(17), 10269–10273.

Fattore, L., Fadda, P., Spano, M. S., Pistis, M., & Fratta, W. (2008). Neurobiological mechanisms of cannabinoid addiction. *Molecular and Cellular Endocrinology*, *286S*, S97–S107.

Gerdeman, G. L., & Lovinger, D. M. (2003). Emerging roles for endocannabinoids in long-term synaptic plasticity. *British Journal of Pharmacology*, *140*(5), 781–789.

Gilman, J. M., Kuster, J. K., Lee, S., Lee, M. J., Kim, B. W., Makris, N., … Breiter, H. C. (August 16, 2014). Cannabis use is quantitatively associated with nucleus accumbens and amygdala abnormalities in young adult recreational users. *The Journal of Neuroscience*, *34*(16), 5529–5538.

Grace, A., Floresco, S. B., Goto, Y., & Lodge, D. J. (2007). Regulation offering of dopaminergic neurones and control of goal-directed behaviors. *Trends in Neurosciences*, *30*(5), 220–227.

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

Heimer, L., Zahm, D. S., Churchill, L., Kalivas, P. W., & Wohltmann, C. (1991). Specificity in the projection patterns of accumbal core and shell in the rat. *Neuroscience*, *41*, 89–125.

Hoffman, A. F., Riegel, A. C., & Lupica, C. R. (2003). Functional localization of cannabinoid receptors and endogenous cannabinoid production in distinct neuron populations of the hippocampus. *European Journal of Neuroscience*, *18*(3), 524–534.

Ikemoto, S., Qin, M., & Liu, Z. H. (2005). The functional divide for primary reinforcement of D-amphetamine lies between the medial and lateral ventral striatum: is the division of the accumbens core, shell and olfactory tubercle valid. *The Journal of Neuroscience*, *25*, 5061–5065.

Iversen, L. (2003). Cannabis and the brain. *Brain*, *126*, 1252–1270.

Jhou, T. C., Fields, H. L., Baxter, M. G., Saper, C. B., & Holland, P. C. (2009). The rostromedial tegmental nucleus (RMTg), a major GABAergic afferent to midbrain dopamine neurones, selectively encodes aversive stimuli and promotes behavioral inhibition. *Neuron*, *61*(5), 786–800.

Koob, G. F., & Le Moal, M. (2001). Drug addiction, dyes regulation of reward, and allostasis. *Neuropsychopharmacology*, *24*, 97129.

Kortleven, C., Fasano, C., Thibault, D., Lacaille, J. C., & Trudeau, L. E. (May 2011). The endocannabinoid 2 arachidonoylglycerol inhibits long-term potentiation of glutamatergic synapses onto ventral tegmental area dopamine neurones in mice. *European Journal of Neuroscience*, *33*(10), 1751–1760.

Laviolette, S. R., Gallegos, R. A., Henriksen, S. J., & van der Kooy, D. (2004). Opiate state controls bi-directional reward signaling via GABAA receptors in the ventral tegmental area. *Nature Neuroscience*, *7*, 160–169.

Leweke, F., & Koethe, D. (2008). Cannabis and psychiatric disorders: it is not only addiction. *Addiction Biology*, *13*, 264–275.

Lupica, C. R., Riegel, A. C., & Hoffman, A. F. (2004). Marijuana and cannabinoid regulation of brain reward circuits. *British Journal of Pharmacology*, *143*, 227–234.

Lupica, C. R., Riegel, A. C. (June 2005). Endocannabinoid release from midbrain dopamine neurons: a potential substrate or cannabinoid receptor antagonist treatment of addiction. *Neuropharmacology*, *48*(8), 1105–1116.

Melis, M., Pistis, M., Perra, S., Muntoni, A. L., Pillola, G., & Gessa, G. L. (January 7, 2004). Endocannabinoids mediate presynaptic inhibition of glutamatergic transmission in rat ventral tegmental area dopamine neurones through activation of CB1 receptors. *The Journal of Neuroscience*, *24*(1), 53–62.

Nader, K., & Van der Kooy, D. (1997). Deprivation state switches the neurobiological sub- strates mediating opiate reward in the ventral tegmental area. *The Journal of Neuroscience*, *17*, 383–390.

Overton, P. G., & Clark, D. (1997). Burst firing in midbrain dopaminergic neurones. *Brain Research Reviews*, *25*(3), 312–334.

Piercea, R. C., & Kumaresana, V. (2006). The mesolimbic dopamine system: the final common pathway for the reinforcing effect of drugs of abuse? *Neuroscience and Biobehavioral Reviews*, *30*, 215–223.

Plescia, F., Brancato, A., Marino, R. A., Vita, C., Navarra, M., & Cannizzaro, C. (2014). Effect of acetaldehyde intoxication and withdrawal on NPY expression: focus on endocannabinoidergic system involvement. *Frontiers in Neuroscience*, *7*(64), 1–9.

Riegel, A. C., & Lupica, C. R. (December 8, 2004). Independent presynaptic and postsynaptic mechanisms regulate endocannabinoid signaling at multiple synapses in the ventral tegmental area. *The Journal of Neuroscience*, *24*(49), 11070–11078.

Serpelloni, G., Diana, M., Gomma, M., & Rimondo, C. (2011). *Cannabis and harm to health*. Italy: Department of Anti-Drug Policy, Presidenza del Consiglio dei Ministri.

Shen, W., Flajolet, M., Greengard, P., & Surmeier, D. J. (August 8, 2008). Dichotomous dopaminergic control of striatal synaptic plasticity. *Science*, *321*(5890), 848–851.

Spiga, S., Lintas, A., Migliore, M., & Diana, M. (2010). Altered architecture and functional consequences of the mesolimbic dopamine system in cannabis dependence. *Addiction Biology*, *15*(3), 266–276.

Spiga, S., Talani, G., Mulas, G., Licheri, V., Fois, G. R., Muggironi, G., … Diana, M. (September 2, 2014). Hampered long-term depression and thin spine loss in the nucleus accumbens of ethanol-dependent rats. *Proceedings of the National Academy of Sciences of the United States of America*, *111*(35), E3745–E3754.

Svizenska, I., Dubovy, P., & Sulcova, A. (2008). Cannabinoid receptors 1 and 2 (CB1 and CB2), their distribution, ligands and functional involvement in nervous system structures: a short review. *Pharmacology, Biochemistry, and Behavior*, *90*, 501–511.

Tan, H., Ahmad, T., Loureiro, M., Zunder, J., & Laviolette, S. R. (2014). The role of cannabinoid transmission in emotional memory formation: implications for addiction and schizophrenia. *Frontiers in Psychiatry*, *5*, 73. http://dx.doi.org/10.3389/fpsyt.2014.00073.

UNODC. (2014). *World drug report 2014*. Vienna: United Nations Office on Drug and Crime.

Urban, N. B. L., Slifstein, M., Thompson, J. L., Xu, X., Girgis, R. R., Raheja, S., … Abi-Dargham, A. (2012). Dopamine release in chronic cannabis users: a [11C]raclopride positron emission tomography study. *Biological Psychiatry*, *71*, 677–683.

Wilson, D. M., Varvel, S. A., Harloe, J. P., Martin, B. R., & Lichtman, A. H. (2006). SR 141716 (Rimonabant) precipitates withdrawal in marijuana-dependent mice. *Pharmacology, Biochemistry, and Behavior*, *85*(1), 105–113.