Chapter 75

Role of the Endocannabinoid System and Major *Cannabis* Constituents in the Reconsolidation and Extinction of Rewarding Drug-Associated Memories

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Abbreviations

2-AG 2-Arachidonoylglycerol
5-HT1A receptor Serotonin type-1A receptor
AEA Anandamide
AM251 *N*-(Piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide
AM630 6-Iodo-2-methyl-1-[2-(4-morpholinyl)ethyl]-1*H*-indol-3-yl-(4 methoxyphenyl) methanone
cAMP Cyclic adenosine monophosphate
CB1 receptor Cannabinoid type-1 receptor
CB2 receptor Cannabinoid type-2 receptor
CBD Cannabidiol
CNS Central nervous system
CPP Conditioned place preference
CS Conditioned stimulus
eCB Endocannabinoid
FAAH Fatty acid amide hydrolase
GPCR G-protein-coupled receptor
GPR55 Orphan G-protein-coupled receptor
LTD Long-term depression
LTP Long-term potentiation
MAGL Monoacylglycerol lipase
NAc Nucleus accumbens
PFC Prefrontal cortex
PPAR Peroxisome proliferator-activated receptor
PTSD Posttraumatic stress disorder
SR141716A Rimonabant hydrochloride
THC Δ^9-Tetrahydrocannabinol
TRPV1 Transient receptor potential vanilloid type-1
URB597 Cyclohexylcarbamic acid 3′-(aminocarbonyl)-[1,1′-biphenyl]-3-yl ester
US Unconditioned stimulus
VTA Tegmental ventral area
WAY 100635 *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-2-pyridinylcyclohexanecarboxamide maleate salt
WIN 55,212 (*R*)-(+)-WIN 55,212

INTRODUCTION

Addiction has been defined as repetitive and compulsive drug use, despite its severe and negative consequences. Although methadone has been used medically to treat heroin (opiate) addiction and therapeutic interventions for nicotine withdrawal (smoking cessation) have been developed, very few medications are available and effective in attenuating permanently addiction to a given drug. Moreover, a high rate of drug relapse is a pervasive problem because, even after years of abstinence, it can occur when an addict encounters cues, including people, objects, or places, associated with prior drug experience. The formation and maintenance of strong associative memories that develop among drug-paired contextual cues and rewarding stimuli or withdrawal-associated aversive feelings have been suggested to contribute to this and other addiction-related outcomes (Foltin & Haney, 2000).

Accumulating evidence now indicates that drugs of abuse are able to induce a dysfunctional synaptic plasticity in brain regions responsible for processing reinforcement and reward aspects. For this reason, addiction may represent inappropriate and maladaptive learning and memory processing (Torregrossa, Corlett, & Taylor, 2011), similar to that underlying other psychiatric conditions such as posttraumatic stress disorder (PTSD) (Parsons & Ressler, 2013). Based on this fact, it would be interesting to establish the effectiveness of therapeutic interventions targeting the maintenance (reconsolidation) and/or suppression (extinction) of aberrant and enduring emotional memories.

The aim of this chapter is to provide an updated overview of the role of the endocannabinoid (eCB) system in learning and memory aspects relevant to drug addiction and traumatic events,

and compare potentially promising findings from preclinical pharmacological studies targeting reconsolidation with those that have shown interference with the extinction of emotional memories.

ESSENTIAL ASPECTS ABOUT LEARNING AND MEMORY PROCESSING

Acquisition and Consolidation

More than a century has passed since the memory consolidation theory was proposed by Müller and Pilzecker (1900). On such occasion, it was found, in humans, that recently acquired information could be disrupted by learning new information immediately after the previous acquisition. Based on that evidence, the authors suggested that at the beginning memories are fragile, but become stable over time. They referred to this period of stabilization as consolidation (McGaugh, 2000). Therefore, whereas acquisition refers to the first stage of learning, consolidation refers to the progressive postacquisition stabilization of the memory trace (Roedirger, Dudai, & Fitzpatrick, 2007). Memory consolidation depends on the activity of the dorsal hippocampus, the amygdala nuclei, and the neocortex (Einarsson & Nader, 2012; McGaugh, 2000), where protein synthesis is required to induce the synaptic plasticity necessary to reinforce the neuronal circuit used for learning (McGaugh, 2000). Of note, activation of neural components of the mesocorticolimbic dopaminergic pathway by drugs of abuse enhances memory consolidation (Blaiss & Janak, 2006). Moreover, one of the most accepted mechanisms proposed to support memory consolidation is long-term potentiation (LTP), which increases synaptic efficacy after the delivery of a relevant stimulus (Bliss & Collingridge, 1993). This premise is supported by results showing that interventions that affect LTP also disrupt memory consolidation (Martin & Shapiro, 2000).

Retrieval

Accessing information stored as memory is a two-step process. The first is reactivation, which represents the passage from a stable to a labile form of the memory trace (Lewis, 1979). Memory reactivation can be succeeded by the expression of a behavior (and/or by verbalization in humans). Retrieval of a previously consolidated memory in the absence of reinforcement can lead the memory to undergo two distinct and independent processes, namely reconsolidation and extinction. The duration of the reexposure to the conditioned stimulus is one of the factors governing the occurrence of memory reconsolidation or extinction (Torregrossa & Taylor, 2013) (Figure 1).

Reconsolidation

As mentioned earlier, memory reactivation renders the memory trace labile, opening an opportunity to modify the original content of the memory. This opportunity is time-limited and is followed by a new restabilization phase known as reconsolidation (Alberini & LeDoux, 2013). Importantly, although consolidation and reconsolidation share some molecular mechanisms, they are considered different memory phases. It has been proposed that the reconsolidation process maintains a memory over time and/or allows its updating (Tronson & Taylor, 2007). The latter aspect is of particular interest owing to the therapeutic potential of disrupting the reconsolidation of cue-drug memories as an anti-relapse treatment for drug addiction (Milton & Everitt, 2012; Tronson & Taylor, 2007).

Extinction

Extinction is a form of inhibitory learning that suppresses the expression of the original memory. The extinction process does not generally modify the original conditioned stimulus–unconditioned stimulus (CS–US) association. It is used by therapists exposing patients to drug or threat cues, promoting the formation of a new and neutral associated memory (Conklin & Tiffany, 2002). In laboratory animals, memory extinction is induced by long retrieval sessions without the presentation of the CS. Despite extinction training, spontaneous recovery of the original memory, as well as its reinstatement and/or renewal, can still occur (Conklin & Tiffany, 2002).

OVERVIEW OF THE ENDOCANNABINOID SYSTEM

As illustrated in Figure 2, the eCB system comprises two different cannabinoid receptors, their endogenous ligands, and the enzymes involved in the synthesis and degradation of these eCBs (Di Marzo, 2009). Cannabinoid type-1 (CB1) and type-2 (CB2)

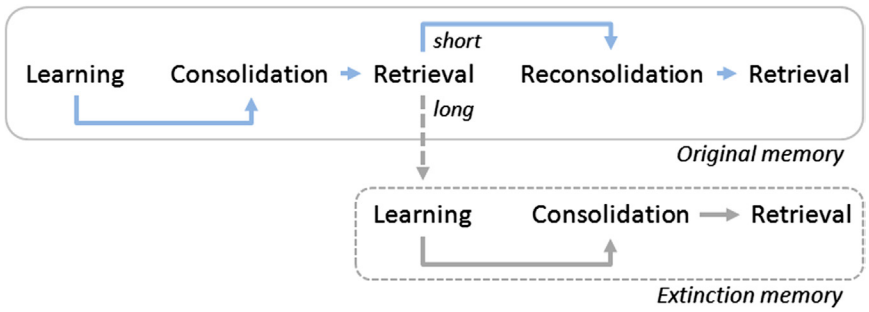

FIGURE 1 Phases of emotional (rewarding or aversive) memory processing and its extinction.

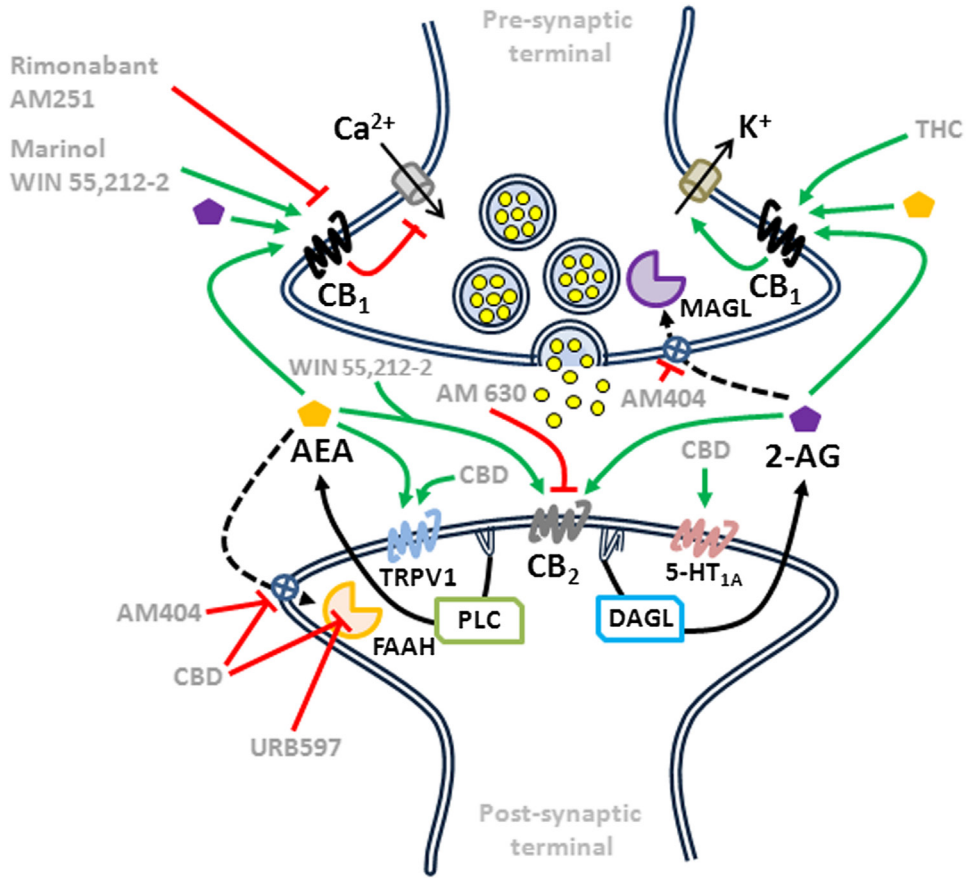

FIGURE 2 The brain eCB system and its main pharmacological targets. The eCBs are produced on demand in postsynaptic terminals: anandamide (AEA) is generated by phospholipase C (PLC), and 2-arachidonoylglycerol (2-AG) is generated by diacylglycerol lipase (DAGL). AEA and 2-AG diffuse retrogradely toward the synaptic cleft where, similar to certain phytocannabinoids (e.g., Δ^9-tetrahydrocannabinol, THC) and synthetic cannabinoids (e.g., WIN 55,212-2 and marinol), they activate presynaptic metabotropic CB1 receptors and/or postsynaptic metabotropic CB2 receptors, which are significantly less abundant than CB1 receptors in the brain. Stimulation of presynaptic CB1 receptors reduces the release of stored neurotransmitter by opening inwardly rectifying K^+ channels and closing Ca^{2+} channels. AEA and 2-AG may reenter post- or presynaptic nerve terminals, possibly through a specialized transporter that can be blocked by AM404, after which they are respectively catabolized by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL). AM251 and rimonabant (SR141716) are CB1 receptor antagonists and AM630 is a CB2 receptor antagonist. Cannabidiol (CBD) is a phytocannabinoid that acts through multiple mechanisms of action, including inhibition of FAAH activity and AEA reuptake and activation of serotonin type-1A (5-HT1A) receptors and transient receptor potential vanilloid 1 (TRPV1) channels. See the text for additional details.

receptors have different densities and distributions in the central nervous system (CNS) and peripheral tissues. CB1 receptors are expressed by central and peripheral neurons, while CB2 receptors are expressed mostly by immune cells, although they are also expressed in the brain (Van Sickle et al., 2005). Initially, CB2 receptors were found in the brain only under pathological conditions (Ibrahim et al., 2003). However, further investigation has revealed expression of CB2 receptors in several brain regions under physiological conditions (Van Sickle et al., 2005), including those related to reward processing, such as the nucleus accumbens (NAc), which may suggest they contribute to drug addiction (Aracil-Fernández et al., 2012; Xi et al., 2011).

The two major endogenous ligands for CB1 and CB2 receptors are anandamide (AEA) and 2-arachidonylglycerol (2-AG). These eCBs are synthesized on demand, mainly postsynaptically, and act as retrograde messengers regulating the presynaptic release of various neurotransmitters (Castillo, Younts, Chávez, & Hashimotodani, 2012). AEA acts as a partial agonist at both CB1 and CB2 receptors (selectivity: CB1>>CB2) and activates transient receptor potential vanilloid type 1 (TRPV1) channels (Starowicz, Nigam, & Di Marzo, 2007). 2-AG is the most abundant eCB in the CNS and nonselectively activates CB1 and CB2 receptors (Castilo et al., 2012; Di Marzo, 2009). It has been shown that AEA, 2-AG, and Δ^9-tetrahydrocannabinol (THC), the main psychotomimetic constituent of *Cannabis*, exert their effects mainly through activation of CB1 receptors (Castilo et al., 2012). In the case of eCBs, the effects are rapidly terminated through carrier-mediated uptake followed by intracellular enzymatic degradation. 2-AG and AEA are metabolized by monoacylglycerol lipase and fatty acid amide hydrolase (FAAH), respectively (Wilson & Nicoll, 2002).

The eCBs function as retrograde signaling messengers, regulating neuronal activity and plasticity by depolarization-induced suppression of inhibition or excitation (Wilson & Nicoll, 2002). Both phenomena are forms of short-term synaptic plasticity that contribute to the regulation of a number of physiological functions, including motivation, memory, and emotions (Di Marzo,

2009; Maldonado, Valverde, & Berrendero, 2006). Additionally, eCBs appear to modulate the memory process by changing synaptic plasticity and mediating more persistent forms of synaptic plasticity (LTP and long-term depression (LTD)) in several addiction- and memory-related brain areas (Maldonado et al., 2006; Sidhpura & Parsons, 2011).

USING THE CONDITIONED PLACE PREFERENCE PARADIGM TO INVESTIGATE THE ROLE OF THE ENDOCANNABINOID SYSTEM IN MEMORY RECONSOLIDATION AND EXTINCTION

Conditioned place preference (CPP), the most widely used paradigm to investigate hedonic memory reconsolidation and extinction, is a form of Pavlovian conditioning used to measure the reward and motivational aspects of drug abuse. The CPP apparatus has two distinct compartments or chambers. When a given chamber of the CPP apparatus is paired with a rewarding drug (e.g., amphetamine, cocaine, or morphine), the animal will show a preference for the associated compartment (Tzschentke, 2007). It is still not clear which psychological processes underlie place preference. Furthermore, the CPP task does not exactly reflect the extent of Pavlovian conditioning that occurs between environmental CS and the effects of a drug in human addicts who have an extensive history of drug use and therefore many pairings of CS and US. Despite these translational constraints, preclinical studies focusing on reconsolidation of rewarding drug memory have used the CPP procedure. Importantly, studies of memory require a change in animal behavior. Thus, the formation and storage of associative memories can be attributed to the expression of CPP (Tzschentke, 2007).

As illustrated in Figure 3, a typical protocol for studying memory reconsolidation or extinction using CPP involves three phases: training (or conditioning), retrieval, and testing, which is usually conducted within days or weeks postretrieval. In the first phase, the animals are trained to acquire drug-associative memories and then, following either extinction or forced abstinence, they are subjected to a retrieval session. Memory retrieval is triggered by reexposure to a CS, commonly without a US presentation. Thus, memories that were already consolidated can be retrieved and reactivated, becoming susceptible to disruption, if a reconsolidation blocker is present at the time of reactivation, or to facilitation, if an extinction facilitator is present (Nader, Schafe, & LeDoux, 2000).

ROLE OF THE ENDOCANNABINOID SYSTEM IN LEARNING AND MEMORY PROCESSING

CB1 receptors are highly abundant in brain areas, such as the NAc, ventral tegmental area (VTA), prefrontal cortex (PFC), amygdala, hippocampus, and dorsal striatum (Maldonado et al., 2006), responsible for learning and memory and drug-related behaviors (Robbins, Ersche, & Everitt, 2008). Importantly, brain-imaging studies in humans have revealed a similar neuroanatomical involvement in cue-elicited craving in drug addicts (Volkow, Fowler, & Wang, 2004).

The eCB system is involved in the primary rewarding effects of various drugs of abuse (alcohol, cannabinoids, nicotine, and opioids), possibly by increasing the firing rate of dopaminergic neurons of the mesolimbic pathway. For instance, the activation of CB1 receptors located on axon terminals of γ-aminobutyric acid (GABA)-ergic neurons in the VTA inhibits GABA transmission, removing the inhibitory input on dopaminergic neurons and leading to increased dopamine activity (Maldonado et al., 2006). Similarly, glutamatergic neurotransmission from neurons of the NAc is also modulated by the activation of CB1 receptors (Maldonado et al., 2006; Sidhpura & Parsons, 2011). The inhibition of glutamate release attenuates the excitation of GABAergic neurons from the NAc that project to the VTA, thus indirectly activating VTA dopaminergic neurons.

The impact of CB2 receptors on the reinforcing effects of drugs has also been described (Aracil-Fernández et al., 2012; Xi et al., 2011). Overall, these preclinical studies report that brain CB2 receptors interfere with drug-rewarding effects. Their activation within dopamine terminals could potentially inhibit dopamine release and, thus, reduce the reinforcing properties of cocaine (Aracil-Fernández et al., 2012; Xi et al., 2011). If so, these findings raise several new hypotheses to be tested subsequently, including whether this regulation of dopamine release by CB2 receptors could modulate the intake of other drugs of abuse and whether this action is evident in other animal models.

The eCB system also modulates the motivation to drug-seeking behavior, which is predictive of drug relapse, by a mechanism unrelated to the release of dopamine in the NAc (Maldonado et al., 2006). The PFC is a brain area that integrates sensory information, emotional processing, and hedonic

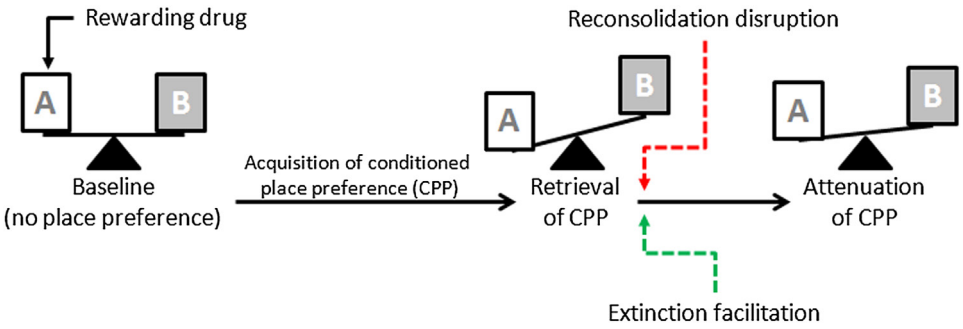

FIGURE 3 Postretrieval (pharmacological and/or behavioral) strategies to attenuate drug rewarding-related memories using the CPP paradigm in laboratory animals.

experience. It seems that activation of CB1 receptors in the PFC could explain the eCB system's involvement in the motivation to seek a drug (Kringelbach, 2005).

The eCB system has been implicated in relapse and drug-seeking behavior, probably by influencing the synaptic plasticity underlying drug-related memories. Convergent evidence has shown that the eCB-mediated LTD in the NAc, amygdala, hippocampus, PFC, and VTA is critical in preparing excitatory synapses for subsequent induction of LTP, which in turn contributes to consolidation of the reward-driven behavior required to establish the addictive process (Maldonado et al., 2006; Sidhpura & Parsons, 2011).

Although the involvement of the eCB system in emotional learning and memory is complex, there is agreement in the literature about the eCB system's role as a promoter of memory extinction, at least for aversive memories (Pamplona, Bitencourt, & Takahashi, 2008; Suzuki et al., 2004). Accordingly, either genetic or pharmacologic blockade of CB1 receptors impairs extinction of classical fear conditioning (Pamplona et al., 2008; Suzuki et al., 2004). On the other hand, these experimental interventions did not affect those memories produced by appetitive or drug-related stimuli (Harloe, Thorpe, & Lichtman, 2008; Manwell et al., 2009). Scarce evidence is currently available about the effects of cannabinoids on the reconsolidation of hedonic and aversive memories. Since impairing the reconsolidation produces longer lasting effects than facilitating the extinction process, interest in the mechanisms of reconsolidation has increased since 2005.

THE ENDOCANNABINOID SYSTEM AND RECONSOLIDATION OF REWARDING DRUG-RELATED MEMORIES

So far, studies have shown that systemic administration of the CB1 receptor antagonist rimonabant disrupts drug reward-associated memory. Indeed, it was demonstrated in rats that antagonism of CB1 receptors persistently impaired the reconsolidation of methamphetamine- (Yu et al., 2009), nicotine- (Fang et al., 2011), and morphine-induced CPP (De Carvalho, Pamplona, Cruz, & Takahashi, 2014) (Table 1). Activation of CB1 and CB2 receptors by WIN 55,212-2 did not alter morphine-induced CPP, but potentiating eCB signaling by inhibiting AEA metabolism promoted a transient and CB1 receptor-dependent increase in morphine-induced CPP (De Carvalho et al., 2014). It was also shown that systemic injection of AM630, a selective CB2 receptor antagonist, had no effect on the reconsolidation of morphine-induced CPP (De Carvalho et al., 2014). Of note, it is possible that the lack of effect of AM630 may be attributed to its relatively poor pharmacokinetic properties and/or blood–brain barrier passage (Xi et al., 2011). Some studies have shown that CB2 receptor activation reduces drug-related behavior in rodents (Aracil-Fernández et al., 2012; Xi et al., 2011). Altogether, these findings indicate that pharmacological manipulation of CB2 receptors could represent a potential target for drug addiction-related memory mitigation, even though further investigation is needed to corroborate this premise.

TABLE 1 Cannabinoid Effects on Rewarding Drug and Appetitive Memory Extinction and Reconsolidation

Drug/Route	Reconsolidation Effect	Extinction Effect	Species	Learning Task	References
Rimonabant (CB1 antagonist, systemic)	↓	○	Rat	Amphetamine; morphine; nicotine CPP	Manwell et al. (2009), Yu et al. (2009), Fang et al. (2011), and De Carvalho et al. (2014)
Rimonabant (CB1 antagonist, systemic)	—	○	Mice	Appetitively motivated operant conditioning task	Niyuhire et al. (2007)
AM630 (CB2 antagonist, systemic)	○	—	Rat	Morphine CPP	De Carvalho et al. (2014)
WIN 55,212-2 (CB1/CB2 agonist, systemic)	○	—	Rat	Morphine CPP	De Carvalho et al. (2014)
URB597(FAAH inhibitor, systemic)	↑	↑	Rat	Naloxone-precipitated morphine withdrawal; morphine CPP	Manwell et al. (2009) and De Carvalho et al. (2014)
CBD (not CB1/CB2, systemic)	—	↑	Rat	Cocaine or amphetamine CPP; Intravenous heroin self-administration	Parker, Burton, Sorge, Yakiwchuk, and Mechoulam (2004) and Ren, Whittard, Higuera-Matas, Morris, and Hurd (2009)
THC (not CB1/CB2, systemic)	—	↑	Rat	Cocaine or amphetamine CPP	Parker et al. (2004)

CPP, conditioned place preference; ↑, facilitating; ↓, impairing; ○, no effect; —, not evaluated.

THE ENDOCANNABINOID SYSTEM AND RECONSOLIDATION OF AVERSIVE MEMORIES

PTSD is frequently induced by exposure of individuals to an intense traumatic situation. Patients suffering from this psychiatric condition frequently and spontaneously retrieve the traumatic memory in an intrusive manner, which causes reexperience of the trauma and the expression of hyperarousal, avoidance, increased stress responses, and generalization. This has a deep impact on the individual's life and, to relieve these symptoms, PTSD patients tend to increase their use of addictive drugs (Müller et al., 2014). In this regard, it becomes clear that the reconsolidation of trauma-related memories could be a target for pharmacological interventions able to disrupt this memory restabilization phase and, consequently, ameliorate their corresponding symptoms (Alberini & LeDoux, 2013).

It has been shown in mice previously conditioned to contextual cues that activation of CB1 receptors is necessary to induce memory labilization (Suzuki, Mukawa, Tsukagoshi, Frankland, & Kida, 2008). However, the role of AEA and 2-AG in memory labilization is still unknown. Of note, PTSD patients exhibit low levels of AEA and present an upregulation of CB1 receptors (Neumeister, 2013).

Activation of CB1 receptors by AEA in the dorsal hippocampus of rats disrupts the reconsolidation of contextual fear memory (de Oliveira Alvares, Pasqualini Genro, Diehl, Molina, & Quillfeldt, 2008). Also in rats, infusing the agonist WIN 55,212-2 into the amygdala blocks the reconsolidation of fear-potentiated startle (Lin, Mao, & Gean, 2006). The drug also blocked the reconsolidation of conditioned taste aversion when infused into the intrainsular cortex (Kobilo, Hazvi, & Dudai, 2007). WIN 55,212-2 is a potent CB1/CB2 agonist and, although CB2 receptors are less expressed than CB1 receptors in the brain, some participation of CB2 receptors cannot be ruled out. There have been only a few other studies investigating the role of the eCB system in fear memory reconsolidation (Table 2). Overall, their results are consistent, suggesting that activation of this modulatory system could control the intensity of fear memories by blocking the reconsolidation step each time they are retrieved.

EFFECTS OF Δ^9-TETRAHYDROCANNABINOL AND CANNABIDIOL ON RECONSOLIDATION OF DRUG, APPETITIVE, AND AVERSIVE MEMORIES

The two main phytocannabinoids of *Cannabis* are the psychotomimetic THC and the nonpsychotomimetic CBD. Since their discovery, the pharmacological effects of THC and CBD have been extensively characterized in laboratory animals and humans.

Preclinical studies investigating the effects of these two phytocannabinoids on memory extinction and reconsolidation are still scarce. One study (Parker, Burton, Sorge, Yakiwchuk, & Mechoulam, 2004) investigated the effects of a low dose of THC (0.5 mg/kg) on extinction of cocaine- and amphetamine-induced CPP in rats. The authors reported a facilitated extinction that was not blocked by antagonism of CB1 receptors with rimonabant, suggesting a mechanism not dependent on the eCB system. Regarding THC's effects on aversive memories, a study with rats that received a dose of 10 mg/kg THC once per day for 6 days reported impaired extinction of an auditory fear memory (Ashton, Smith, & Darlington, 2008). In contrast, a study with healthy humans subjected to classical fear conditioning reported that 7.5 mg/kg THC induced a better recall of extinction than controls. This effect was accompanied by increased activity in brain regions that process fear extinction, suggesting that the eCB system, or at least CB1 receptors, may be a potential target for pharmacological interventions to attenuate PTSD and other memory-related disorders (Rabinak et al., 2013). Altogether, the data about THC and extinction point to a possible use of low doses of THC for rewarding drug- or aversive-associated memories. A recent preclinical study has reported an impairing effect of THC (0.3-10 mg/kg i.p.) on fear memory reconsolidation in rats. This effect was prevented by pharmacological antagonism of CB1 receptors located in prelimbic subregion of the medial prefrontal cortex (Stern et al., 2015). There has still been no study aimed at investigating the effects of THC on the reconsolidation of drug rewarding-related memories.

In rodents, a low dose of CBD (5.0 mg/kg) has been shown to facilitate the extinction of both cocaine- and amphetamine-induced CPP (Parker et al., 2004). Like THC, this CBD effect was unrelated to CB1 receptor activation. A lack of hedonic effects of CBD was also shown, demonstrating that it does not induce addiction (Parker et al., 2004). This result is reinforced by the study of Katsidoni, Anagnostou, and Panagis (2013) showing that CBD did not affect the reinforcing effect of brain stimulation in rats. Rather, it prevented the rewarding effects of morphine, but not cocaine, an effect mediated through serotonin type-1A (5-HT1A) receptors (Katsidoni et al., 2013). The same dose of CBD also reduced heroin-seeking behavior reinstated in animals exposed to a conditioned cue, but did not change their self-intake of heroin, the extinction behavior, or the drug seeking induced by a prime heroin injection, suggesting CBD as an antirelapse drug (Ren et al., 2009).

A randomized double-blind placebo-controlled study demonstrated that the inhalation of CBD during 1 week reduced cigarette consumption in a long-lasting manner (Morgan, Das, Joye, Curran, & Kamboj, 2013). Although the authors did not investigate the mechanisms underlying this effect, they suggested a possible impairing effect of CBD on the reconsolidation process. Reinforcing the potential therapeutic effects of CBD, a study demonstrated that humans exposed to a transdermal gel containing 5% of CBD presented nearly 50% less neurodegeneration induced by alcohol binge consumption than controls (Liput, Hammell, Stinchcomb, & Nixon, 2013).

Infusing CBD into the brain ventricles (2.0 μg/μl) also facilitates contextual fear-conditioning extinction in rats, an effect blocked by the CB1 receptor antagonist rimonabant (Bitencourt et al., 2008). Another preclinical study reported an impairing effect of CBD (10 mg/kg) on fear memory reconsolidation in rats. This effect was blocked by the CB1 receptor antagonist AM251, but not by the 5-HT1A antagonist WAY 100635 (Stern et al., 2012). Although the effect of CBD in both extinction and reconsolidation could be prevented by CB1 receptor blockade, it is known that CBD is not a direct CB1 receptor agonist. Thus, it is thought to inhibit the activity of FAAH, with a consequent increase in the level of AEA (Bisogno et al., 2001). As AEA activates CB1 receptors and TRPV1 channels (Starowickz et al., 2007), a possible

TABLE 2 Cannabinoid Effects on Aversive Memory Extinction and Reconsolidation

Drug/Route	Reconsolidation Effect	Extinction Effect	Species	Learning Task	References
CB1 deletion	—	↓	Mice	Auditory fear conditioning	Marsicano et al. (2002), Kamprath et al. (2006), and Plendl and Wotjak (2010)
Rimonabant (CB1 antagonist, systemic)	↑	↓	Mice	Auditory fear conditioning; contextual fear conditioning; fear-potentiated startle; inhibitory avoidance	Marsicano et al. (2002), Suzuki et al. (2004), Chhatwal, Myers, Ressler, and Davis (2005), Niyuhire et al. (2007), Pamplona, Prediger, Pandolfo, and Takahashi (2006), and Pamplona et al. (2008)
Rimonabant (CB1 antagonist, insular cortex)	○	↓	Rat	Conditioned-taste aversion	Kobilo et al. (2007)
AM251 (CB1 antagonist, infralimbic cortex, amygdala, dorsal hippocampus)	↓↑	↓	Rat	Fear-potentiated startle; contextual fear conditioning	Bucherelli, Baldi, Mariottini, Passani, and Blandina (2006), de Oliveira Alvares et al. (2008), and Lin et al. (2006)
WIN 55,212-2 (CB1/CB2 agonist, systemic, dorsal hippocampus, amygdala, insular cortex)	↓	↑	Rat	Contextual fear conditioning; inhibitory avoidance; fear potentiated Startle; conditioned-taste aversion	Pamplona et al. (2006, 2008), Lin et al. (2006), Kobilo et al. (2007), and Abush and Akirav (2010)
Anandamide (endogenous CB1 agonist, dorsal hippocampus)	↓	↑	Rat	Contextual fear conditioning	de Oliveira Alvares et al. (2008)
AM404 (Anandamide uptake inhibitor, systemic, icv, infralimbic cortex, intra CA1)	—	↑	Rat	Contextual fear conditioning; inhibitory avoidance, fear-potentiated startle	Bitencourt, Pamplona, and Takahashi (2008), Pamplona et al. (2008), Abush and Akirav (2010), Chhatwal et al. (2005), and Lin et al. (2006)
URB597 (FAAH inhibitor, infralimbic cortex)	—	↑	Rat	Fear-potentiated startle	Lin et al. (2006)
CBD (CB1 indirect agonist, icv, systemic)	↓	↑	Rat	Contextual fear conditioning	Bitencourt et al. (2008) and Stern, Gazarini, Takahashi, Guimarães, and Bertoglio (2012)
CBD (mechanism not evaluated, oral)	—	↑	Human	Fear conditioning	Das et al. (2013)
THC (mechanism not evaluated, systemic for six days)	—	↓	Rat	Auditory fear conditioning	Ashton, Smith, and Darlington (2008)
Marinol (Synthetic THC, mechanism not evaluated, oral)	—	↑	Human	Fear conditioning	Rabinak et al. (2013)
THC (mechanism not evaluated, oral)	—	○	Human	Fear conditioning	Klumpers et al. (2012)

↑, facilitating, ↓, impairing, ○, no effect, —, not evaluated, icv, intracerebroventricularly.

contribution to the latter cannot be excluded in advance. Despite the convergent evidence mentioned above, as yet no clinical study has investigated whether CBD can impair the reconsolidation (or facilitate the extinction) of drug- and trauma-related memories.

The studies reviewed herein indicate that more than one mechanism of action may be recruited by THC and/or CBD to induce their cognitive effects, which depend at least in part on the nature (rewarding vs aversive) of the memory evaluated. A mechanism relying on indirect CB1/CB2 activation could explain CBD's effects on extinction and reconsolidation of aversive memories, probably by an increase in AEA induced by FAAH inhibition. In support of this premise, increasing the endogenous levels of AEA in the brain facilitates the extinction and impairs the reconsolidation of fear memories (Bitencourt et al., 2008; Lin et al., 2006; de Oliveira Alvares et al., 2008; Pamplona et al., 2008). As mentioned earlier, however, the effects of THC and CBD on the extinction of drug-related memories appear to be unrelated to CB1 receptor-mediated signaling mechanisms. Possible candidates to be investigated are the 5-HT1A receptor and TRPV1 channels. Regarding THC, there are few and contradictory results and, like CBD, there appear to be multiple mechanisms of action mediating its effects on memory extinction and reconsolidation.

To summarize, whereas the available preclinical data provide evidence that CBD, which does not induce addiction by itself and can counteract the negative effects of THC (Niesink & van Laar, 2013), is able to attenuate rewarding drug- and fear-related memories through extinction facilitation and/or reconsolidation disruption, the effects of THC on these matters require further investigation.

CONCLUDING REMARKS

At present, numerous studies indicate that the reward caused by consuming drugs can pathologically usurp neural mechanisms of learning and memory. The CPP paradigm has been extensively used in drug addiction research to investigate reward-related learning and memory processes. Preclinical research focusing on the reconsolidation of drug rewarding-associated memories, particularly through manipulation of the eCB system, is still scarce, but evidence provided so far supports their relationship. The data reviewed herein also indicate that disruption of reconsolidation can be achieved by direct or indirect activation of brain CB1 receptors. Altogether, these findings support the notion that the eCB system mediates relapse episodes following cessation of drug exposure, highlighting the view that reconsolidation blockade, rather than extinction facilitation, may indicate a new direction for the treatment for drug- and context-induced relapse to drug seeking. However, further studies are necessary to elucidate the exact mechanisms by which the eCB signaling system modulates these processes.

APPLICATIONS TO OTHER ADDICTIONS AND SUBSTANCE MISUSE

Accumulating evidence has also pointed to a role for the eCB system in other types of addiction, such as those associated with food intake and gambling. Indeed, a dysfunctional eCB signaling seems to contribute not only to food addiction, by controlling appetite and food preference, but also to gambling, by controlling risk behaviors. Overall, it is thought these nondrug addictions also usurp the brain natural reward system and involve aberrant learning and memory processing. For that reason, the potential relevance of targeting the eCB system at specific time points, such as reconsolidation, to their treatment should be further investigated.

Current drug addiction treatments effectively relieve craving in the clinical context, but not when addicts return to their usual environment, as exposure to stimuli associated with the effects of the drug trigger the addict's habitual response of using the drug once again. Thus, disrupting reconsolidation of drug cues may boost conventional cue-exposure therapy's effectiveness, holding promise for a more effective treatment to addiction. In this context, whereas studies addressing the misuse of CNS stimulants are more numerous, those focusing on CNS depressants with potential of abuse and addiction are scarcer. In either case, however, modulating the activity of the eCB system may have a potential therapeutic value to the treatment of drug addiction, presenting promising applicability to the clinical setting once it theoretically targets the core of the problem, the formation and maintenance of an aberrant and enduring rewarding memory.

DEFINITION OF TERMS

Aversive memory This refers to a memory from a stressful life experience.

Conditioned stimulus This is an early neutral stimulus that is associated with a US or a reinforcer.

Conditioned place preference This is a form of Pavlovian conditioning used for assessing rewarding and motivational properties of drug abuse.

Extinction This refers to a new and inhibitory memory that suppresses the original one.

Memory This is the retention of internal representations generated by one or several experiences that can subsequently drive behavior.

Memory consolidation This refers to the progressive postacquisition stabilization phase of a memory trace.

Pavlovian conditioning This is a type of associative learning in which a previously motivationally neutral (conditioned) stimulus is paired in space and time with a motivationally relevant US (aversive or hedonic). The behavior of the individual does not affect the contingency between the presentations of both stimuli.

Reconsolidation This represents the restabilization phase of a memory that may occur after its retrieval and reactivation.

Retrieval This refers to the time point at which an established memory is accessed.

Retrograde messenger This is a neurotransmitter released by the postsynapse that travels backward and activates presynaptic receptors.

Reward This is a stimulus that induces hedonic pleasure.

Unconditioned stimulus This is a stimulus that is motivationally relevant to the individual (e.g., food, sex).

KEY FACTS OF MEMORY RECONSOLIDATION

- Around 1965 it was demonstrated that previously consolidated memories can be impaired by amnesic interventions when they are in a labile state again, as is the case during retrieval and

reactivation. These reactivated memories may undergo a process of restabilization, known as reconsolidation, to be maintained. For historical reasons, however, research on memory reconsolidation remained scarce for several decades.

- Since 2000, this process has been demonstrated for various types of memory, principally those with negative or positive emotional valence. Moreover, convergent evidence obtained from studies using laboratory animals and humans has implicated several brain regions (e.g., amygdala, hippocampus, and PFC) and neurotransmitters/neuromodulators (e.g., glutamate, GABA, noradrenaline, glucocorticoids, and eCBs) in memory reconsolidation.
- Accumulating evidence supports the theory that reconsolidation may offer an opportunity to update aberrant memories, such as those underlying addiction and PTSD. The capacity for plastic changes in memory strength or content following memory retrieval/reactivation is currently being investigated as a new target to improve the therapeutic interventions into these neuropsychiatric disorders.
- At least at the preclinical level, several boundary conditions may constrain memory reconsolidation. Overall, this process takes place when there is a prediction error (a discrepancy between actual and expected events) during its retrieval/reactivation. Moreover, it is favored when retrieval of the memory trace is short and when it is not so remote and/or strong.
- These and related issues have started to be addressed in human studies, thus increasing our understanding of the reconsolidation phenomenon and, in particular, its potential value in the permanent treatment of dysfunctional memory processes in mental disorders.

SUMMARY POINTS

- Drug addiction is a chronic, relapsing disorder, at least in part owing to the formation and maintenance of a strong memory that associates drugs and environmental cues.
- Interfering with the reconsolidation process has been proposed as a potential therapeutic strategy to attenuate and perhaps even erase aberrant memories underlying drug addiction and PTSD.
- eCBs are retrograde messengers that mediate the reinforcing effects of the drug of abuse and enhance synaptic plasticity in brain regions involved in the etiology of drug addiction.
- The eCB system participates in the common neurobiological mechanisms that underlie learning, memory, and drug-related behaviors.
- Pharmacologically manipulating the eCB system may be a promising therapeutic approach to disrupting the reconsolidation of hedonic or aversive memories, such as those experienced by people suffering from drug addiction or PTSD, respectively.
- CBD is a nonpsychotomimetic phytocannabinoid of potential relevance in attenuating cue-induced drug-seeking behavior and fear-related memories through extinction facilitation or reconsolidation disruption.

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