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Acute blockade of CB1 receptor leads to reinstatement of MDMA-induced conditioned place preference

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ABSTRACT

Cannabis is one of the drugs most commonly consumed in combination with ecstasy (3,4-methylenedioxy-methamphetamine, MDMA). Although numerous studies have attempted to further our understanding of the role of the cannabinoid system in drug abuse, few have focused on how it influences the rewarding effects of MDMA. The aim of the present study was to evaluate the role of the CB1 cannabinoid receptor in vulnerability to reinstatement of a MDMA-induced conditioned place preference (CPP). Mice were first conditioned with 5 mg/kg of MDMA. Once the preference had been extinguished, a priming dose of MDMA, alone or plus the CB1 cannabinoid agonist WIN 55,212-2 (0.1 and 0.5 mg/kg) or the CB1 cannabinoid antagonist SR 141716A (0.3 mg/kg), was administered on alternate days. The CB1 receptor antagonist, alone or with any of the priming doses of MDMA, induced reinstatement of the preference. In contrast, WIN 55,212-2 had no effect on reinstatement of the MDMA-induced CPP when administered alone, but potentiated the effects of subthreshold priming doses of MDMA. These results highlight the important role of the CB1 receptor in vulnerability to reinstatement of drug-seeking behavior and point to the importance of the endocannabinoid system in the addictive potential of MDMA.

1. Introduction

Recent reports indicate that almost 90% of ecstasy users (in the age range of 15–64 years old) also consume cannabis, which make it the drug most widely consumed with MDMA, followed by alcohol, tobacco and cocaine (UNODC World Drug Report, 2010). The endocannabinoid system is certainly the primary site of action of the rewarding and pharmacological responses induced by cannabinoids (Ledent et al., 1999), but it also exerts a general modulatory effect on the reward circuitry and is involved in the rewarding and addictive properties of some drugs of abuse. By regulating the reward circuits of the brain (Lupica et al., 2004; Gardner, 2005), endocannabinoid signaling is involved in almost all stages of the addiction cycle, from the maintenance of stably acquired addictive behavior (Le Foll and Goldberg, 2005) to relapse to drug-seeking following abstinence (Fattore et al., 2007a, 2007b). For instance, CB1 receptor agonists, such as THC or WIN 55,212-2, can promote the rewarding effects of different drugs, including heroin (Solinas et al., 2005), nicotine (Valjent et al., 2002), alcohol (Gallate et al., 1999; Colombo et al., 2002) and cocaine (Fattore et al., 1999).

Cannabinoids exert their effects through interactions with specific endogenous CB1 and CB2 cannabinoid receptors (Devane et al., 1988; Munro et al., 1993) that are present in mammalian tissues. The cannabinoid receptor CB1 is highly expressed in the brain and mediates most, if not all, of the psychoactive/central effects of cannabis (Maldonado et al., 2006; Fattore et al., 2008; Solinas et al., 2008). The CB1 receptors are localized preferentially at the presynaptic level; thus, it is believed that they inhibit the release of glutamate, GABA and other neurotransmitters (Schlicker and Kathmann, 2001; Wilson and Nicoll, 2002), including DA and 5-HT (Giuffrida et al., 1999; Nakazi et al., 2000; Gardner, 2005; Fattore et al., 2007a; Solinas et al., 2008), which are key components of the mechanism of action of MDMA and represent a common neurobiological substrate of the addictive properties of different drugs of abuse (Maldonado et al., 2006; Parolaro and Rubino, 2008).

MDMA and cannabinoid agonists such as WIN 55212-2 produce reinforcing effects in mice and rats when administered alone (Manzanedo et al., 2004, 2010; Daza-Losada et al., 2007; Zarrindast et al., 2007). Indeed, evidence has shown that MDMA's stimulation of 5-HT neurotransmission represents a neurochemical mechanism that reduces the severity of cannabinoid withdrawal syndrome (Touriño et al., 2007). Furthermore, several physiological responses mediated by

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MDMA administration, including locomotor activity, body temperature, mood, learning and reward, are also modulated by the endocannabinoid system (Piomelli, 2005; Giuffrida et al., 1999). CB1 cannabinoid receptors are implicated in the reinforcing effects of MDMA (Braida and Sala, 2002; Braida et al., 2005; Touriño et al., 2008). In a previously published study CB1 knockout mice did not acquire self-administration behavior at any of the doses of MDMA administered (0.03, 0.06, 0.12 and 0.25 mg/kg/infusion), though the drug did induce conditioned place preference (CPP) and enhanced extracellular levels of DA in the nucleus accumbens of mutant mice (Touriño et al., 2008). In addition, infusion of the cannabinoid agonist CP 55,940 has been shown to reduce i.c.v. MDMA self-administration (Braida and Sala, 2002), while an MDMA-induced conditioned place preference (CPP) was undermined by cannabinoid (SR 141716A), opioid (naloxone), and serotoninergic (tropisetron) antagonists (Braida et al., 2005), thus suggesting that multiple receptor systems contribute to the expression of MDMA-induced incentive motivation.

In a recent report, we have shown that WIN 55212-2 increases the rewarding effects of MDMA (1.25 mg/kg), but only at low doses. Interestingly, SR 141716 also increased the rewarding effects of the lowest MDMA dose administered and did not block the effects of WIN 55,212-2 (Manzanedo et al., 2010). We have also observed that the reinforcing effects of MDMA are enhanced in mice exposed to the cannabinoid agonist WIN 55,212-2 during adolescence. This pretreatment also increases vulnerability to the reinstatement of an MDMA-induced CPP after a priming dose of either MDMA or WIN (Rodríguez-Arias et al., 2010), which suggests that pre-exposure to cannabinoids strengthens the reinforcing properties of MDMA and renders subjects more vulnerable to drug-induced reinstatement.

Animal models of reinstatement are used to study relapse to drug-seeking and drug-taking behavior following a period of drug abstinence, in some cases prolonged. These protocols allow this particular aspect of the addiction cycle, which seems to be the core of the addictive process, to be investigated. Pre-clinical studies have shown how endocannabinoid signaling is an essential part of the re-initiation of drug-seeking and -taking behaviors. Priming with CB1 agonists can reinstate the extinguished self-administration not only of cannabinoids (Spano et al., 2004), but also of heroin (De Vries et al., 2003; Fattore et al., 2003), cocaine (De Vries et al., 2001) and alcohol-containing solutions (McGregor et al., 2005), while blockade of CB1 receptors prevents drug- and/or cue-induced reinstatement of cannabinoid (Spano et al., 2004), heroin (Fattore et al., 2005), nicotine (De Vries et al., 2005; Shoaib, 2008), alcohol (Cippitelli et al., 2005; Economidou et al., 2006) and methamphetamine (Anggadiredja et al., 2004).

In previous studies we have observed that the ability of WIN 55212-2 to reinstate an MDMA-induced CPP in mice depends on the animal's past experience of this cannabinoid agonist. When animals had no previous experience, WIN 55212-2 was not capable of reinstating the extinguished preference of MDMA-induced CPP, although a WIN 55,212-2-induced CPP was reinstated by priming doses of MDMA (Manzanedo et al., 2010). However, when mice were exposed to WIN 55212-2 prior to developing an MDMA-induced CPP, this cannabinoid agonist strongly reinstated the extinguished preference (Rodríguez-Arias et al., 2010). In this way, available evidence points to a role for the cannabinoid system in the reinforcing effects of MDMA and in drug-induced reinstatement of MDMA-seeking behavior.

No studies have evaluated the function of the cannabinoid system during reinstatement of MDMA-seeking. The aim of the present study was to explore the role of the CB1 cannabinoid receptor in the reinstatement of a MDMA-induced CPP. To do this, the effects of the selective CB1 agonist WIN 55212-2 and the highly potent CB1 antagonist/inverse agonist SR 141716A were evaluated once the preference of a MDMA-induced CPP had been extinguished. Their ability to induce reinstatement and their effect on the reinstatement induced by a priming injection of MDMA were evaluated.

2. Materials and methods

2.1. Subjects

A total of 140 male mice of the OF1 strain were acquired commercially from Charles River (Barcelona, Spain) at 21 days of age (postnatal day 21 (PD21)). They were housed in groups of four in plastic cages (25×25×14.5 cm) during the 8 days prior to initiation of experiments, under the following conditions: constant temperature (21±2 °C), a reversed light schedule (white lights on: 19.30–07.30 h), and food and water available ad libitum, except during behavioral tests. Animals were handled on two consecutive days before the preconditioning (Pre-C) phase in order to reduce their stress levels in response to experimental manipulations. Procedures involving mice and their care were conducted in compliance with national, regional and local laws and regulations, which are in accordance with the European Communities Council Directives (86/609/EEC, 24 November 1986).

2.2. Drugs

Animals were injected intraperitoneally with 0.6, 1.25, 2.5 or 5 mg/kg of MDMA (±3,4-methylenedioxymetamphetamine hydrochloride, Laboratorios Lipomed AG, Switzerland), 0.1 or 0.5 mg/kg of WIN 55212-2 (Tocris, Biogen Científica, S.L., Madrid, Spain), or 3 mg/kg of SR 141716A (Sanofi Recherche, Montpellier, France) in a volume of 0.01 ml/g. Control groups were injected with the physiological saline used to dissolve the drugs (NaCl 0.9%) or with Tween-80 (Sigma-Aldrich, Madrid, Spain), which was used to dissolve WIN 55212-2 and SR 141716A (two drops of Tween dissolved in saline).

2.3. Procedure of CPP

2.3.1. Acquisition

Place conditioning consisted of three phases and took place during the dark cycle following an unbiased procedure in terms of initial spontaneous preference (for more details see Daza-Losada et al., 2007). In brief, during pre-conditioning (Pre-C) mice were allowed access to both compartments of the apparatus for 900 s on 3 consecutive days. On day 3, the time spent by the animal in each compartment during the 900 s period was recorded. In each group, half the animals received the drug or vehicle in one compartment and the other half in the other compartment. Data analysis (one-way ANOVA) revealed no significant differences in the time spent in the drug-paired and vehicle-paired compartments during the pre-conditioning phase. In the second phase (conditioning), animals were conditioned with MDMA or saline through four pairings with the respective compartment (one pairing per day). Those conditioned with MDMA received an injection of MDMA (5 mg/kg) on days 4, 6, 8 and 10 immediately prior to being confined to the drug-paired compartment for 30 min, and received physiological saline on days 5, 7, 9 and 11 before being confined to the vehicle-paired compartment for 30 min. Control animals received an injection of physiological saline before being confined for 30 min to one of the compartments on days 4, 6, 8 and 10 and to the other on days 5, 7, 9 and 11. The central area was made inaccessible during conditioning by lowering the guillotine doors. During the third phase, or post-conditioning (Post-C), which took place on day 12, the guillotine doors separating the two compartments were removed and the time spent by the untreated mice in each compartment was recorded during an observation period of 900 s. The difference in seconds between the time spent in the drug-paired compartment during the Post-C test and that spent in the same compartment during the Pre-C test is a measure of the degree of conditioning induced by a drug. If this difference is positive, then the drug has induced a preference for the drug-paired compartment, whereas the opposite indicates the induction of an aversion.

2.3.2. Extinction

Conditioned groups underwent a daily extinction session that consisted of placing animals in the apparatus (without the guillotine doors separating the compartments) for 900 s until the time spent in the drug-paired compartment by each group was similar to that of Pre-C and different from that of the Post-C test. Thus, all the animals in each group were submitted to the same number of extinction sessions, independently of their individual scores. Saline-conditioned groups underwent only one extinction session to confirm the lack of CPP. The extinction of CPP was always confirmed in a subsequent session 24 h after the last extinction session.

2.3.3. Reinstatement

The effects of a priming dose were evaluated 24 h after confirmation of extinction. The reinstatement test was the same as that for Post-C (free ambulation for 900 s), except that animals were tested 15 min after administration of the respective dose of MDMA. Reinstatement of the preference was induced by 0, 0.625, 1.25 or 2.5 mg/kg of MDMA alone (**M0; M0.6; M1.25; M2.5**), in combination with 0.1 or 0.5 mg/kg of WIN 55212-2 (M0-W0.1; M0.6-W0.1; M1.25-W0.1; M2.5-W0.1; M0-W0.5; M0.6-W0.5; M1.25-W0.5; M2.5-W0.5), or in combination with 3 mg/kg of SR 141716A (M0-SR3; M0.6-SR3; M1.25-SR3, M2.5-SR3). Both WIN 55212-2 and SR 141716A were administered 15 min before MDMA.

2.3.4. Statistical analysis

Data relating to the time spent in the drug-paired compartment were analyzed using an analysis of variance (ANOVA) for repeated measures. A two-way ANOVA for each MDMA dose employed (0, 0.612, 1.25, or 2.5 mg/kg) during the reinstatement test was performed, with a "between" subject variable — "drug", with four levels: Saline, WIN 0.1, WIN 0.5 and SR — and a "within" subject variable — "days" with four levels: Pre-C, Post-C, extinction and reinstatement. The Bonferroni adjustment was employed for post hoc multiple comparisons.

3. Results

The results for the groups that did not receive MDMA in the reinstatement test are shown in Fig. 1. The ANOVA revealed a significant effect of the variable "days" [$F(3,32) = 23{,}265$; $p<0.001$], as more time was spent in the drug-paired compartment in the Post-C test than in the Pre-C and extinction tests ($p<0.001$ and $p<0.01$, respectively). A significant effect was also observed with respect to the interaction "days × drug" [$F(3,34) = 3{,}308$; $p<0.05$]. All groups developed CPP with 5 mg/kg of MDMA ($p<0.001$ for the M0 and M0-W0.5 groups, $p<0.01$ for the M0-SR3 group, and $p<0.05$ for the M0-W0.1 group); however, only the M0-SR3 group spent more time in the drug-paired compartment in the reinstatement test than during the Pre-C and extinction tests ($p<0.05$). Moreover, this group presented higher scores than the M0 group in the reinstatement test ($p<0.05$).

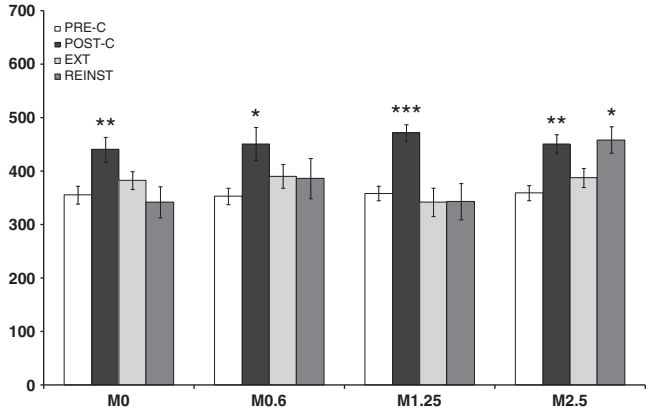

Fig. 1. Effects of a priming dose of vehicle (M0 = 10) or, 0.6 (M0.6 = 8), 1.25 (M1.25 = 9), or 2.5 (M2.5 = 10) mg/kg of MDMA, on the reinstatement of a conditioned place preference induced by 5 mg/kg of MDMA. *** $p<0.001$; ** $p<0.01$; * $p<0.05$, significant difference in the time spent in Pre-C vs Post-C sessions or reinstatement tests.

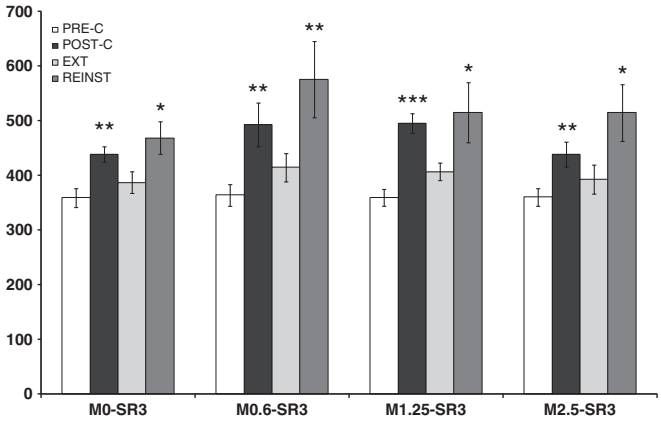

Fig. 2. Effects of 3 mg/kg of SR 141716A, alone (M0-SR3 = 9) or in combination with a priming dose of 0.6 (M0.6-SR3 = 8), 1.25 (M1.25-SR3 = 8) or 2.5 (M2.5-SR3 = 11) mg/kg of MDMA, on the reinstatement of a conditioned place preference induced by 5 mg/kg of MDMA. SR 141716A was administered 15 min before the priming dose of MDMA. *** $p<0.001$; ** $p<0.01$; * $p<0.05$, significant difference in the time spent in Pre-C vs Post-C sessions or reinstatement tests.

Fig. 2 shows the results obtained in the animals treated during the reinstatement test with 0.612 mg/kg of MDMA alone or in combination with cannabinoid compounds (M0.6; M0.6-W0.1; M0.6-W0.5; M0.6-SR3). The ANOVA revealed significant differences for the variable "days" [$F(3,26) = 15{,}709$; $p<0.001$], with more time being spent in the drug-paired compartment during the Post-C test than during the Pre-C and Extinction phases ($p<0.001$ for Post-C vs Pre-C and Extinction tests, $p<0.05$ for Reinstatement vs Pre-C test). A significant effect was also observed for the interaction "days × drug" [$F(3,28) = 6{,}025$; $p<0.01$]. All the groups showed higher values during the Post-C test than in the Pre-C test ($p<0.01$ for M0.6-SR3; $p<0.05$ for the rest of the groups); however, only the M0.6-SR3 group spent more time in the drug-paired compartment in the reinstatement test than during the Pre-C and Extinction tests ($p<0.001$). Furthermore, this group presented higher scores in the reinstatement test than the M0.6-W0.1 group ($P<0.01$).

The results for the groups that received a priming dose of 1.25 mg/kg of MDMA, alone or in combination with cannabinoid compounds (M1.25, M1.25-W0.1, M1.25-W0.5, and M1.25-SR3), are

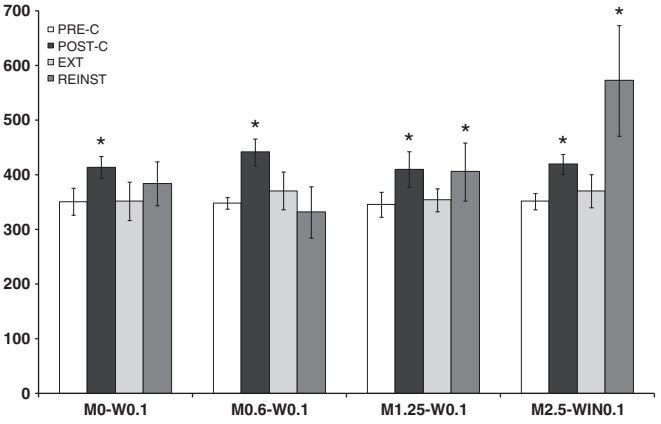

Fig. 3. Effects of 0.1 mg/kg of WIN 55212-2, alone (M0-W0.1 = 8) or in combination with a priming dose of 0.6 (M0.6-W0.1 = 8), 1.25 (M1.25-W0.1 = 8) or 2.5 (M2.5-W0.1 = 8) mg/kg of MDMA, on the reinstatement of a conditioned place preference induced by 5 mg/kg of MDMA. WIN 55212-2 was administered 15 min before the priming dose of MDMA. * $p<0.05$, significant difference in the time spent in Pre-C vs Post-C sessions or reinstatement tests.

shown in Fig. 3. The statistical analysis revealed significant differences for the variable "days" [F (3,31) = 21.023; p<0.001], with more time being spent in the drug-paired compartment during the Post-C and reinstatement tests than during the Pre-C and Extinction tests (p<0.001). A significant effect was also observed for the interaction "days × drug" [F(9,99) = 2.836; p<0.05]. All the groups showed higher values during the Post-C test than in the Pre-C test (p<0.001 for M1.25 and M1.25-SR3; p<0.05 for the rest of the groups). Administration of SR 141716A and either of the two doses of WIN 55212-2 produced reinstatement of the MDMA-induced place preference (p<0.01 for the M1.25-W0.5 group and p<0.05 for the rest, with respect to the extinction test). Furthermore, in the reinstatement test, the M1.25-SR3 group showed higher values than the group that had received 1.25 mg/kg of MDMA (p<0.01).

Fig. 4 shows the groups that received a priming dose of 2.5 mg/kg of MDMA alone or plus cannabinoid compounds. The ANOVA performed for the groups M2.5, M2.5-W0.1, M2.5-W0.5 and M2.5-SR3 revealed a significant effect of the variable "Days" [F(3,35) = 22,086; p<0.001]. Animals spent more time in the drug-paired compartment during the Post-C and Reinstatement tests than during the Pre-C and Extinction tests (p<0.001). In addition, more time was spent in the drug paired compartment during the reinstatement test than during the Post-C test (p<0.05).

4. Discussion

The results of the present study confirm the complex interaction that takes place between the cannabinoid system and MDMA. Acute blockade of the endocannabinoid system with SR 141716A induced the reinstatement of MDMA-induced preference, even in the absence of a priming dose of the drug. An extinguished MDMA-induced CPP was reinstated after administration of 3 mg/kg of SR 141716A, which demonstrated that cross-reinstatement occurred between MDMA and the cannabinoid antagonist. This interaction was also evident in the fact that SR 141716A induced reinstatement when administered with sub-threshold doses of MDMA (0.625 and 1.25 mg/kg). On the other hand, the stimulation of CB1 receptors resulted in a non-effective priming dose of MDMA producing an effect. WIN 55212-2, which did not induce any effect when administered alone, led to reinstatement when administered with a 1.25 mg/kg priming dose of MDMA that was not effective by itself.

Adolescence is a developmental period during which individuals are highly vulnerable to the consequences of exposure to drugs of abuse

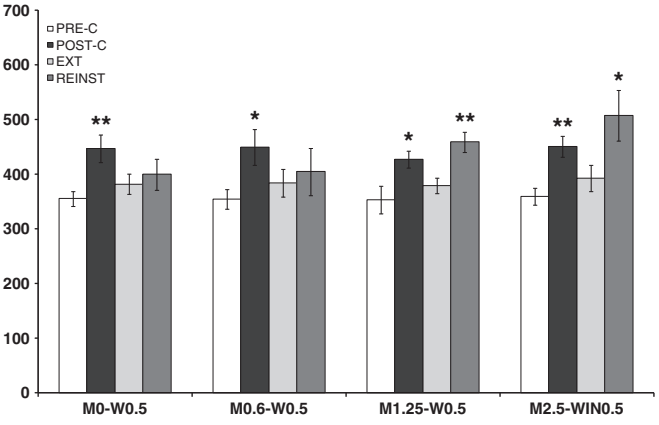

Fig. 4. Effects of 0.5 mg/kg of WIN 55212-2, alone (M0-W0.5 = 11) or in combination with a priming dose of 0.6 (M0.6-W0.5 = 8), 1.25 (M1.25-W0.5 = 8) or 2.5 (M2.5-W0.5 = 8) mg/kg of MDMA, on the reinstatement of a conditioned place preference induced by 5 mg/kg of MDMA. WIN 55212-2 was administered 15 min before the priming dose of MDMA. **p<0.01, *p<0.05, significant difference in the time spent in Pre-C vs Post-C sessions or reinstatement tests.

(Schneider, 2008). Given that adolescent animals were employed in the present study it is important to bear in mind the numerous maturational processes that occur in the endocannabinoid system during this critical period and which leave the still-developing brain highly susceptible to cannabis exposure. Evidence indicates that adolescents are also vulnerable to the onset of several neuropsychiatric disorders, of which drug addiction is an example (Chambers et al., 2003). Recent epidemiological evidence of a strong association between cannabis use during adolescence and an increased risk of developing schizophrenia implicates the endocannabinoid system in these processes (Moore et al., 2007). The CB1 cannabinoid receptor is highly expressed in the prefrontal cortex (Bodor et al., 2005), and this cortical region undergoes widespread structural and molecular refinements during the adolescent transition period (Spear, 2000). Indeed, an age-dependent down-regulation of cortical CB1 expression, most distinctive in the prefrontal cortex, has recently been reported (Heng et al., 2011). On the other hand, several reports have shown that exposure to MDMA during adolescence can result in mitochondrial oxidative damage to the central nervous system (Alves et al., 2009).

The mechanism by which MDMA and cannabinoids interact is not altogether clear. MDMA raises the level of dopamine by increasing their release through an inhibition of both their uptake and MAO metabolism (Mørland, 2000). On the other hand, cannabinoids participate in the regulation of dopamine synthesis, release and turnover (Gardner and Vorel, 1998). The overlapping expression of cannabinoid and dopamine receptors that occurs in some brain areas, including the NAcc (Hermann et al., 2002), suggests that the reinforcing properties of MDMA can be modified by an interaction with these cannabinoid receptors. This interaction can modify their respective functions, with important behavioral and pharmacological consequences (Martín et al., 2008). The endocannabinoid system acts as a modulator of dopaminergic neurotransmission, thus undermining dopaminergic function (Rodríguez de Fonseca et al., 1994, 1998; Ferrer et al., 2007). The dopaminergic neurons of the mesocorticolimbic pathway are controlled by excitatory and inhibitory inputs modulated by CB1 cannabinoid receptors (Maldonado et al., 2006). The endogenous cannabinoid system seems to be a negative modulator of dopamine D1 and D2 receptor-mediated behaviors through its actions on neurons that express dopamine receptors (Martín et al., 2008). The effects of CB1 receptor antagonists in the striatum are thought to abolish the inhibitory influence of endogenous CB1 receptor agonists on striatal dopamine D1 and D2 receptor function (Rodríguez de Fonseca et al., 1994, 1998; Sañudo-Peña et al., 1998; Giuffrida et al., 1999). Moreover, potentiation of endogenous cannabinoid signaling blocks dopamine D1 receptor-mediated grooming and D2 receptor-mediated oral stereotypes. In addition, contralateral turning induced by unilateral intrastriatal infusion of D1 receptor agonists is counteracted by the anandamide uptake blocker AM404 and potentiated by the cannabinoid antagonist SR141716A. In light of these effects, we hypothesize that acute blockade of CB1 receptors by SR 141716A triggers the dopaminergic function of the inhibitory endogenous cannabinoid tone, which in turn induces the reinstatement of the MDMA-seeking behavior. A previous report in which intraacumbal SR 141716A induced place preference has provided support for this hypothesis (Sañudo-Peña et al., 1997). Another recent study has confirmed this effect and has demonstrated that glutamate receptors participate in SR 141716A - mediated place preference, which was abolished when AMPA glutamate receptors were blocked (Ramiro-Fuentes et al., 2010).

Another important result of the present study is the lack of effect observed with the cannabinoid agonist WIN 55,212-2, which did not induce reinstatement of the extinguished CPP when administered alone. This result is in accordance with a previous study in which preference was not reinstated in animals conditioned with 2.5 or 5 mg/kg of MDMA after a priming dose of 0.1 or 0.5 mg/kg of WIN 55212-2 (Manzanedo et al., 2010). Cannabinoid agonists and MDMA possess different neurotransmitter activation profiles, as MDMA is a DA releaser that affects other systems, such as the serotoninergic

system, while cannabinoids seem to play a modulating role in DA transmission. It is also possible that the first exposure to a cannabinoid agonist induces an aversive effect in animals conditioned with MDMA. Conditioned place aversion induced by WIN 55,212-2 has previously been reported (Valjent and Maldonado, 2000), and acute injections of different cannabinoid agonists or THC induce anxiogenic-like behavioral reactions in rodents (Onaivi et al., 1995; Rodríguez de Fonseca et al., 1997). In this context, we have seen that an extinguished MDMA-induced CPP is not reinstated after a priming injection of WIN 55,212-2 in animals with no prior exposure to cannabinoids (Manzanedo et al., 2010), but we have observed the reinstatement of an extinguished MDMA-induced CPP after a priming dose of this cannabinoid agonist in animals previously exposed to several doses of WIN 55,212-2 during adolescence (Rodríguez-Arias et al., 2010). Moreover, it should be taken into consideration that cannabinoids preferentially stimulate the release of DA into the shell of the Nacc; both THC and WIN 55,212-2 induce a pronounced dose-dependent effect in the shell, but only a weak response in the core after administration of high doses (Tanda et al., 1997). Neurocircuitry alterations associated with drug-induced reinstatement after extinction have been linked to a glutamatergic pathway from the prefrontal cortex to the nucleus accumbens core, as well as the projection of dopamine from the VTA to the medial prefrontal cortex, and the projection of GABA from the nucleus accumbens to the ventral pallidum (Kalivas and O'Brien, 2008). The fact that WIN 55,212-2 affects DA in the shell but not in the core of the Nacc must be taken into account when evaluating the lack of an effect observed in the present study with the cannabinoid agonist. In line with these observations, a recent report by Schenk et al. (2011) has pointed to the vital role of DA neurotransmission in MDMA-induced reinstatement, since the D1 receptor antagonist SCH-23390 and the D2 receptor antagonist eticlopride attenuated the reinstatement produced by MDMA.

Although lacking effects when administered alone, WIN 55,212-2 potentiated the reinstating effects of a MDMA-priming dose. When this cannabinoid agonist was administered with a non-effective priming dose of MDMA (1.25 mg/kg) a reinstatement of the preference were observed. Previous reports have shown that a low dose of WIN 55212-2 (0.1 mg/kg) increased the rewarding effects of MDMA when the two drugs were administered simultaneously during the acquisition phase of the CPP (Manzanedo et al., 2010). Robledo et al. (2007) reported similar results when they observed that THC increased the effectiveness of low doses of MDMA in both the CPP and self-administration paradigm.

Administration of WIN 55,212-2 dose-dependently enhanced firing of dopamine neurons in the VTA and increased dopamine concentration in the NAcc shell (Gessa et al., 1998). Administration of the CB1 antagonist SR 141716 prevented these effects, thereby indicating a direct contribution of CB receptor activation to dopamine enhancement. Similarly to the effects of opiates, the mechanism of this increased dopamine release in the NAcc is considered to be modulatory rather than a direct effect on VTA dopamine neurons (Tanda et al., 1997). In this way, the enhanced DA release produced by WIN 55,212-2 should augment the effect of sub-threshold priming doses of MDMA, thereby rendering them effective.

WIN 55,212-2 is generally considered to be a full agonist of CB1 receptors (Murray and Bevins, 2010). However, some studies have indicated a possible action on CB2 receptors (Schlicker and Kathmann, 2001; Ahmed et al., 2010). Recently, the role of CB2 receptors in the stress response has been shown to be critical, as mice that express higher numbers of these receptors exhibit a resistant phenotype (García-Gutiérrez et al., 2010). This role can be considered an additional mechanism through which WIN 55,212-2 favors reinstatement. Additionally, activation of the κ-dynorphin opioid system after WIN 55,212-2 administration has also been described (Mendizábal et al., 2006).

Unlike classic psychomotor stimulants such as amphetamines or cocaine, which readily condition place preference at varying doses and under different conditions, cannabinoid agonists exert more mixed effects (Murray and Bevins, 2010). There are a number of experimental variables that appear to have an impact on the outcome of some studies, including the compound employed and the dose applied, the number of conditioning trials, session length, injection-to-placement interval, and pretreatment. Depending on these experimental parameters, cannabinoids can induce conditioned place preference, aversion or no effect. For instance, the endocannabinoid transport inhibitor AM404 induces CPP in rats housed under enriched conditions, but not in rats kept in standard cages (Bortolato et al., 2006). Altogether, these studies reveal a dose-dependent switch from reward to aversion, with low and high doses of cannabinoids inducing reward and aversion, respectively. An analogous phenomenon has been observed in human addicts, in whom low doses of THC or levonantradol are rewarding and higher doses are aversive (Noyes et al., 1975; Raft et al., 1977; Laszlo et al., 1981). These observations point to the possibility that this cannabinoid antagonist produces rewarding effects, presumably by blocking either a dysphoric action or the inhibition of reward circuits produced by endogenous cannabinoids. Accordingly, Sañudo-Peña et al. (1997) reported that SR 141716A induced place preference in rats, whereas THC produced place aversion or had no effect on a CPP paradigm. In a previous study using the CPP procedure we did not observe any reinforcing effect on SR 141716A, although a strong preference for the compartment paired with the cannabinoid antagonist was noted in most of the treated mice (Manzanedo et al., 2004). However, we have seen that this cannabinoid antagonist increases both the reinforcing effects and vulnerability to reinstatement of an extinguished preference through drug priming when it is administered with a sub-threshold dose of MDMA during the acquisition phase (Manzanedo et al., 2010). Considered as a whole, these results suggest that endogenous cannabinoids act as a counter-reward mechanism or produce aversive motivational states that can be reverted after acute administration of a cannabinoid antagonist.

The results of the present study, in which agonism and antagonism of the CB1 receptor produce similar effects on MDMA-induced CPP, have been previously described with respect to cocaine self-administration. Systemic SR 141716A induced a dramatic dose-dependent decrease in the breakpoint for cocaine in rats undergoing long access self-administration (Orio et al., 2009). Stimulation of CB1 receptors seems to exert similar effects, as AM404, a CB1 direct agonist, attenuates the reduction of the self-stimulation threshold induced by cocaine in rats (Vlachou et al., 2008), and the agonist WIN55,212-2 has also been reported to undermine the reinforcing effects induced by cocaine (Vlachou et al., 2003). When interpreting these results, it should be taken into consideration that SR 141716A, as well as being a CB1 antagonist, also acts as an inverse agonist (Landsman et al., 1997). SR 141716A exerts actions on signal transduction mechanisms when administered in the absence of CB1 receptor stimulation, as it inhibits GTPγS binding and increases cAMP production (Mato et al., 2002). Inverse agonists stimulate signal transduction in the opposite direction to that in which it is stimulated by the agonist. In the case of CB1 receptors, agonists inhibit cyclic-AMP production, while inverse agonists stimulate production of this second messenger (Mato et al., 2002).

CB1 receptors are expressed in many brain regions where they presynaptically regulate both excitatory and inhibitory neurotransmission. A recent report by Bellocchio et al. (2010) suggests that CB1-dependent control of food intake is due to the opposite effect on excitatory glutamatergic transmission and GABAergic transmission. They hypothesise that the orexigenic effect of a low dose of THC is mediated by CB1-dependent inhibition of glutamate release, whereas the hypophagic effect of a higher dose depends on CB1-mediated inhibition of GABA release. The pharmacology of CB1 receptors can vary according to the neuronal populations in which they are expressed, thus determining different cannabinoid-mediated intracellular responses. An alternative explanation is that both types of neurons also mediate

different responses related with reward, which would explain the comparable effects observed after administration of both CB1 agonist and antagonist.

Finally, it is important to bear in mind that exposure to the drug itself, presence of drug-associated stimuli or cues, and exposure to a stressful episode are different events that can lead to reinstatement (Shalev et al., 2002; Shaham et al., 2003; Weiss, 2005). Social and physical stress are capable of inducing reinstatement of morphine-induced CPP (Ribeiro Do Couto et al., 2006), and we have recently found that both kinds of stress can reinstate cocaine- and MDMA-induced CPP (unpublished results). Additionally, as discussed previously, cannabinoid agonists and antagonists/inverse agonists can induce anxiety and stress responses (Navarro et al., 1997). This could constitute another potential mechanism by which these compounds induce reinstatement, thereby altering the emotionality of animals and activating specific pathways of stress-induced reinstatement.

5. Conclusion

The evidence in the literature suggests that cannabinoids affect the rewarding effects of different drugs of abuse, among which ecstasy is not an exception. However, the results published are somewhat controversial and raise new questions. CB1 cannabinoid receptors can modulate the rewarding properties of MDMA depending on the doses employed, the moment at which administration takes place, and the paradigm employed. Our results demonstrate, for the first time, that CB1 receptors are also critical to reinstatement of the MDMA-induced CPP.

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