Cannabinoid Receptor Involvement in Stress-Induced Cocaine Reinstatement: Potential Interaction with Noradrenergic Pathways

Linda K. Vaughn[1], **John R. Mantsch**[1], **Oliver Vranjkovic**[1], **Gregory Stroh**[1], **Margaret LaCourt**[1], **Margaret Kreutter**[1], and **Cecilia J. Hillard**[2]

John R. Mantsch: John.Mantsch@mu.edu; Cecilia J. Hillard: Chillard@mcw.edu

[1]Department of Biomedical Sciences, Marquette University, Milwaukee, 53233, USA

[2]Neuroscience Research Center and Department of Pharmacology and Toxicology, Medical College of Wisconsin, Milwaukee, 53226, USA

Abstract

This study examined the role of endocannabinoid signaling in stress-induced reinstatement of cocaine seeking and explored the interaction between noradrenergic and endocannabinergic systems in the process. A well-validated preclinical model for human relapse, the rodent conditioned place preference assay was used. Cocaine-induced place preference was established in C57BL/6 mice using injections of 15 mg/kg cocaine. Following extinction of preference for the cocaine-paired environment, reinstatement of place preference was determined following 6 min of swim stress, or cocaine injection (15 mg/kg, i.p.). The role of endocannabinoid signaling was studied using the cannabinoid antagonist AM-251 (3 mg/kg, i.p.). Another cohort of mice was tested for reinstatement following administration of the cannabinoid agonist CP 55,940 (10, 20 or 40 μg/kg, i.p.). The alpha-2 adrenergic antagonist BRL-44408 (5 mg/kg, i.p.) with or without CP 55,940 (20 μg/kg) was administered to a third group of mice. We found that: 1) AM-251 blocked forced swim-induced but not cocaine-induced reinstatement of cocaine-seeking behavior; 2) the cannabinoid agonist CP 55,940 did not reinstate cocaine-seeking behavior when administered alone but did synergize with a non-reinstating dose of the alpha-2 adrenergic antagonist BRL-44408 to cause reinstatement. These results are consistent with the hypothesis that stress exposure triggers the endogenous activation of CB1 receptors and that activation of the endocannabinoid system is required for the stress-induced relapse of the mice to cocaine seeking. Further, the data suggests that the endocannabinoid system interacts with noradrenergic mechanisms to influence stress-induced reinstatement of cocaine-seeking behavior.

Keywords

cannabinoids; cocaine; norepinephrine; relapse; stress; conditioned place preference

Corresponding Author: Linda K. Vaughn, Ph.D., Department of Biomedical Sciences, PO Box 1881, Milwaukee, WI 53201, Tel:1-414-288-6566, Fax: 1-414-288-6566, Linda.Vaughn@mu.edu.

Cocaine abuse and dependence are important problems with significant psychosocial, medical and financial implications. One of the more troubling aspects of addiction is the persistent vulnerability to relapse to drug use that continues even after long periods of abstinence. Although relapse can be induced by re-exposure to cocaine, drug-associated cues or stress (Childress et al., 1992; See et al., 1999; Shaham et al., 2000; Stewart, 2000; Kalivas and McFarland, 2003), exposure to stress is particularly injurious given its inescapability. The investigation of neurobiological mechanisms at the intersection of motivated behavior and stress could prove fruitful in the search for potential treatments for stress-induced drug relapse. The endocannabinoid system (ECS), including the cannabinoid receptors (CB1 and CB2), endocannabinoids (*N*-arachidonylethanolamine and 2-arachidonoylglycerol) and enzymes and transporters which control synaptic concentrations of endocannabinoids, are attractive targets in this regard.

The preclinical investigation of relapse involves the use of reinstatement protocols in which various stimuli are tested for their ability to re-establish extinguished drug-seeking behavior (Shaham 2003). Conditioned place preference is commonly used to study reinstatement in mice. Using this method, cocaine-induced conditioned place preference becomes extinguished with repeated drug-free exposure to the cocaine-paired environment. The ability of various stimuli to re-establish the cocaine preference is then tested (Tzchentke, 2007). Using this protocol, priming injections of cocaine and a variety of stressors have been shown to produce reinstatement (Itzhak and Martin, 2002; Kreibich and Blendy, 2004; Ribeiro Do Couto et al., 2006; Tzchentke, 2007; Orsini, et al., 2008; Redila and Chavkin, 2008; Mantsch et al., 2010).

There is strong evidence that the ECS is activated in multiple brain regions involved in addiction by stress exposure (Di et al, 2005; Gorzalka et al., 2008; Patel and Hillard, 2008; Rademacher et al, 2008; Hill et al., 2009). It is hypothesized that the result of this activation in most brain regions is to oppose the effects of stress (Cota 2008; Gorzalka et al., 2008; Hill et al., 2010). For example, CB1 receptor knock out animals have increased basal and stress-induced HPA activity, (Barna et al., 2004; Cota et al., 2007), CB1 antagonists increase basal and stress induced glucocorticoid secretion (Manzanares et al., 1999; Patel et al., 2004; Wade et al., 2006), and CB1 agonists and clearance inhibitors reduce stress-induced glucocorticoid secretion (Patel et al., 2004).

Central noradrenergic systems also play an important role in the physiological response to stress (Abercrombie et al., 1988; Tanaka et al., 1991; Finlay et al., 1995) and interactions between the noradrenergic system and cocaine are well documented (Sofuoglu and Sewell, 2009). Repeated cocaine exposure produces long-lasting adaptations within central noradrenergic systems that can lead to enhanced noradrenergic responsiveness during stress (Belej, et al 1996; Macey, et al 2003; Baumann, et al 2004; Beveridge, et al 2005; Lanteri, et al 2008) and norepinephrine (NE) release is required for stress-induced drug reinstatement using both rat self-administration models (Erb et al., 2000; Leri et al., 2002) and mouse conditioned place preference protocols (Mantsch et al., 2010).

The ECS has a well established role in enhancing the motivational effects and promoting drug seeking and relapse behavior of alcohol, nicotine, opioids and marijuana (Tanda and Goldberg, 2003; Lupica et al., 2004; Gardner, 2005; Cohen et al., 2005). Studies of the role of the ECS in the rewarding aspects of cocaine have shown inconsistent effects (Fattore et al., 1999; Soria et al., 2005; Xi et al., 2008; Wiskerke et al., 2008; Orio et al., 2009) but the ECS seems to play an important role in relapse behavior. DeVries et al., (2001) found that a cannabinoid agonist reinstated cocaine seeking in rats that had been conditioned and extinguished in a self-administration paradigm and that a cannabinoid antagonist prevented cocaine- and cue- but not stress- induced reinstatement of cocaine seeking. Cannabinoid

mechanisms were also implicated in cocaine-primed reinstatement in rats (Xi et al., 2006; Filip et al., 2006). In mice, however, cue-induced but not cocaine-induced reinstatement was blocked by a cannabinoid antagonist (Ward et al., 2009). Surprisingly, given the well-established link between the ECS and stress, there has been only one investigation of the role of stress-induced cocaine reinstatement (De Vries et al., 2001) and there have been no studies on the interaction between the endocannabinoid and noradrenergic systems in stress-induced cocaine relapse.

The purpose of this study was to examine the role of the ECS in cocaine- and stress-induced relapse of cocaine seeking behavior and its interaction with noradrenergic mechanisms in mice using a conditioned place preference reinstatement approach.

Experimental Procedures

Animals

Male C57BL/6 mice, 8-9 weeks old, were purchased from Harlan (Indianapolis, IN). The mice were housed singly in a temperature- and humidity-controlled, AAALAC- accredited animal facility under a 12 h/12 h light/dark cycle (lights on at 7:00 AM) and had access to food and water at all times, except when in the experimental chambers. The animals were acclimatized for one week in the animal care facility before use in the studies. All experiments had been reviewed and approved by the Institutional Animal Care and Use Committee and were carried out in accordance with the Guide for the Care and Use of Laboratory Animals.

Drugs

Cocaine HCl was acquired from the National Institute on Drug Abuse (Bethesda, MD) through the NIDA Drug Supply Program. CP 55,940 and AM-251 were purchased from Sigma-Aldrich (St. Louis, MO) and BRL-44408 maleate was acquired from Tocris Bioscience (Minneapolis, MN). Cocaine and BRL-44408 were dissolved in saline (0.9% NaCl solution) and CP 55,940 and AM-251 were dissolved in a 1:1:18 ratio of ethanol, Cremophor EL (Sigma-Aldrich), and saline. Cocaine and BRL-44408 solutions were administered i.p. in a volume of 0.1 ml/25 g body weight. CP 55,940 and AM-251 were administered i.p. in a volume of 0.1 ml/10 g body weight. Pretreatment times for CP 55,940, BRL-44408 and AM-251 were 30 min.

Equipment

Behavioral testing was conducted using six ENV-3013 three-chambered mouse place preference chambers from Med-Associates, Inc (St. Albans, VT). Two $46.5 \times 12.7 \times 12.7$ cm side compartments were each connected to a 7.2 cm $\times$ 12.7 cm gray-colored center compartment. One side compartment had white walls and a stainless steel mesh floor and the other side compartment had black walls and a stainless steel grid rod floor. The clear tops of the compartments were hinged to permit placement and removal of the mice. Room ceiling lights were turned on and, to balance unconditioned side preference, the black compartments were illuminated with additional suspended lights, providing a total illumination of approximately 300 lux. Automated data collection was accomplished using photobeams (6 beams for the white and black test areas and 2 beams for the center gray area) which were evenly spaced across the length of the chamber and interfaced with a computer containing Med-PC software.

Cocaine-Induced Conditioned Place Preference

Cocaine-induced conditioned place preference was established using an unbiased design in which one of the side compartments was randomly designated as the cocaine compartment

and the other as the saline compartment. On the first day of the procedure, mice were placed into the center compartment of the chamber and provided free access to both side compartments for 30 minutes in the absence of saline or cocaine pretreatment to determine pre-conditioning preference. During the 8-day conditioning phase of the experiment, mice received cocaine (15 mg/kg, ip) and saline injections on alternating days after which time they were confined to the randomly designated treatment-appropriate compartment for 30 minutes. After the final conditioning session, mice were tested for the expression cocaine-induced conditioned place preference by once again placing them into the center compartment of the chamber and providing them with free access to the side compartments for 30 minutes. Conditioned place preference was defined as the change in time spent in the cocaine-paired compartment after conditioning compared to the initial pre-conditioning session. The 15 mg/kg cocaine dose was selected based on previous results (Mantsch et al., 2010).

Extinction

Following conditioning, daily extinction training was conducted. During the extinction sessions, mice were placed into the center compartment and allowed free access to the side compartments for 30 min. Mice underwent daily extinction training until the conditioned place preference for the cocaine-paired compartment during the session was reduced by at least 50%.

Reinstatement Testing

The reinstatement sessions were identical to the extinction sessions except that mice received exposure to stressors and/or drug injections prior to the session. Reinstatement was defined as the increase in time spent in the cocaine-paired compartment on the test day (reinstatement day) compared to the time spent on the cocaine-paired compartment on the previous day (extinction day). Mice were tested more than once for reinstatement, receiving all treatments within a given experiment. The stressors and/or drugs were given in counter-balanced order to avoid potential sequence effects. Reinstatement sessions were separated by additional extinction sessions. Mice were required to reach the extinction criterion once again before the next reinstatement test was conducted.

Forced Swim Stress-Induced Reinstatement Testing

Forced swim stress (FS)-induced reinstatement was examined by placing the mice into a 30 cm h × 20 cm d cylindrical polypropylene container filled with water (20-25° C) for 6 min, 24 min after pretreatment with drug or respective vehicles. Following FS, mice were placed back into their home cages for 1-2 min prior to introduction into the center compartment of the place conditioning chamber for reinstatement testing.

Cocaine-Induced Reinstatement Testing

Reinstatement induced by a cocaine priming injection was tested in mice by injection of 15 mg/kg dose of cocaine i.p. immediately before placement into the center compartment of the place conditioning chamber for reinstatement testing.

Effect of the CB1 Receptor Antagonist, AM-251, on Stress- and Cocaine-Induced Reinstatement

In order to determine if CB1 receptor activation plays a role in stress- or cocaine-induced reinstatement, 24 min prior to forced swim testing or 30 minutes prior to cocaine injection, the mice were injected with AM-251 or vehicle. The mice were also injected with AM-251 or vehicle 30 minutes before testing in order to determine whether the AM-251 or vehicle injection could cause reinstatement. All mice received six treatments (FS+ vehicle, FS

+AM-251, cocaine+vehicle, cocaine+AM-251, AM-251 + vehicle, and vehicle+vehicle) in counterbalanced order. Mice reached extinction criterion before retesting.

Reinstatement by the CB1 Receptor Agonist CP 55,940

In order to determine if CB1 receptor activation alone was sufficient to induced reinstatement, mice were tested for reinstatement in response to the synthetic CB1 receptor agoninst CP 55,940. Thirty minutes prior to testing, mice were injected with vehicle or 10, 20 or 40 µg/kg doses of CP 55,940. All mice received all 4 treatments in counterbalanced order. Mice reached extinction criterion before retesting.

Reinstatement by CP 55,940 in Combination with BRL-44408

Another group of mice were tested for reinstatement by CP 55,940 in combination with a subthreshold dose of the selective alpha-2 adrenergic receptor antagonist and pharmacological stressor, BRL-44408, in order to determine if cannabinoid receptor activation could potentiate a pharmacological stressor-induced reinstatement and whether cannabinoid receptor activation interacted with noradrenergic mechanisms to induce reinstatement. It has been shown previously that a sufficient dose of BRL-44408 can induce reinstatement (Mantsch, et al., 2010). We have found that 5 mg/kg BRL-44408 is a subthreshold dose. Therefore, 20 µg/kg CP 55,940 and 5 mg/kg BRL-44408 were injected i.p. 30 minutes prior to reinstatement testing.

Statistical Data Analyses

Statistical analysis was carried out using SigmaPlot 11 statistical software (Systat Software, San Jose, CA). Data are expressed as mean +/- standard error of the mean. The ability of a drug and/or stress procedure to elicit reinstatement was determined by the difference between the time spent in the cocaine-paired compartment on the day of testing (reinstatement day) and the preceding extinction session (extinction day). Comparisons between effects of different drugs and/or stress on reinstatement were also determined. Statistical significance was determined by two-way repeated measures (RM) ANOVA with post-hoc multiple comparisons using the Holm-Sidak method.

Results

Establishment of cocaine-induced conditioned place preference

Previous studies had determined that 15 mg/kg cocaine dose was optimal for producing conditioned place preference (Mantsch et al., 2010). We found significant cocaine-induced conditioned place preference, defined as an increase in time spent in the cocaine-paired compartment, was observed in each of the experiments (p 0.001 for each experiment). The average number of extinction sessions prior to the first reinstatement test session was 5.9. Nineteen percent of mice were not tested for reinstatement since they did not display cocaine-induced conditioned place preference or failed to reach the extinction criterion.

The effect of AM-251 on stress- and cocaine-induced reinstatement

Reinstatement was tested in mice which had been conditioned to cocaine and whose place preference had been extinguished. Both FS (6 minutes) and cocaine (15 mg/kg, i.p.) produced reinstatement, as indicated by significant increases in time spent on the cocaine-paired side compared to the preceding extinction day (p<0.05 Holm-Sidak following a significant interaction between time (extinction and reinstatement day) and treatment $(F(5,25)=8.142, p<0.001$, two-way RM ANOVA, Figure 1). To determine whether endocannabinoid signaling was involved in either type of reinstatement, the CB1 receptor antagonist AM-251 was injected before FS and cocaine. AM-251 treatment completely

blocked the forced swim-induced reinstatement (no significant difference in the time spent in the cocaine-paired environment between the extinction and reinstatement day within the AM+FS group and a significant effect of treatment within reinstatement days between FS and AM+FS, p<0.05, Holm Sidak). AM-251 treatment did not block cocaine-induced reinstatement (significant effect of time in both Coc and Coc+AM, p<0.05, Holm-Sidak, no significant difference between reinstatement days with Coc vs Coc+AM-251). Neither AM-251 nor vehicle produced any reinstatement when given alone.

The effect of CP 55,940 on reinstatement of place preference for cocaine

Mice which had been conditioned to cocaine and whose place preference had been extinguished were tested with vehicle and three doses of the CP 55,940 to determine if administration of a cannabinoid agonist was sufficient to induce reinstatement of place preference (Figure 2). No reinstatement was observed following 10, 20 or 40 μg/kg administration of CP 55,940 (F(1,21)=0.0875, p=0.776, main effect of time (extinction vs. reinstatement day), two-way RM ANOVA).

The involvement of noradrenergic mechanisms in cannabinoid mediation of cocaine place preference

In order to examine the interaction between cannabinergic and noradrenergic systems in cocaine reinstatement, another group of mice which had been conditioned to cocaine and whose place preference had been extinguished were tested with either 1) vehicle, 2) the alpha-2 adrenergic antagonist BRL-44408 (5 mg/kg, i.p.) or 3) BRL-44408 (5 mg/kg, i.p.) and CP 55,940 (20 μg/kg). BRL-44408 alone did not induce reinstatement but when combined with the non-reinstating dose of CP 55,940, reinstatement was induced (F(2,20)=3.499, p<0.05, main effect of treatment, two-way RM ANOVA followed by Holm-Sidak multiple comparisons, P<0.05, Figure 3).

Discussion

We found that systemic administration of a cannabinoid antagonist can reverse stress- but not cocaine-induced reinstatement of cocaine seeking behavior in male C57Bl/6 mice. Cannabinoid receptors are located in many brain areas involved in stress and addiction (Herkenham et al., 1990; Mailleux and Vanderhaeghen, 1992). They influence the release of multiple neurotransmitters, including GAB A, glutamate, norepinephrine and dopamine (Lopez-Moreno et al., 2008). Given the widespread distribution of cannabinoid receptors and the multiplicity of neurotransmitter systems with which the ECS interacts, it is not surprising that the effects of systemic administration of cannabinoid agonists and antagonists have complex and even contradictory effects on addictive behavior. In particular, several studies which used rats to examine the effect of cannabinoids on cocaine reinstatement using a cocaine self-administration model found that cannabinoid antagonists block cocaine-induced reinstatement (De Vries et al., 2001; Filip et al., 2006 ; Xi et al., 2006) but not stress-induced reinstatement of cocaine seeking behavior (De Vries et al., 2001). In contrast, Ward et al., (2009) found that a cannabinoid antagonist did not block cocaine-induced reinstatement in mice. It is possible that different aspects of endocannabinoid effects on addiction are being revealed in studies that use different species, different tests to measure relapse, different drugs and dosages, and different stress paradigms.

The neurochemical pathways that mediate cocaine- and stress-induced reinstatement are not identical. There is evidence that stress-induced but not cocaine-induced reinstatement involves brain noradrenergic pathways, in particular noradrenergic systems that terminate in the bed nucleus of the stria terminalis (BNST) and central nucleus of the amygdala (Leri et al., 2002). In rat self administration models of cocaine reinstatement, treatments that reduce

noradrenergic signaling, either by blocking beta adrenergic receptors (Leri et al., 2002) or suppressing the release of NE by alpha-2 adrenergic receptor activation (Erb et al 2000), reduce stress-induced but not cocaine-induced reinstatement of cocaine seeking. In addition, Mantsch et al., (2010) reported that beta adrenergic receptor antagonists or drugs that decrease NE release block stress-induced reinstatement but not cocaine-induced reinstatement using the mouse conditioned place preference methodology.

It is possible that the ECS plays a role in stress-induced reinstatement by enhancing the release of NE. We found that systemic injection of the cannabinoid agonist, CP 55,940 could not induce reinstatement when injected alone, but did cause reinstatement when combined with a non-reinstating dose of BRL-44408, an alpha-2A adrenergic antagonist that causes increased release of NE. Stress has been shown to alter endocannabinoid concentrations (Patel and Hillard, 2008; Cota, 2008; Hill et al., 2010) and there is significant interaction between the endocannabinoid and noradrenergic systems. Cannabinoid receptors are present in the locus coeruleus (LC) and nucleus of the solitary tract, noradrenergic brainstem nuclei that project to forebrain areas including the BNST (Herkenham et al., 1991) and electrophysiological studies have demonstrated that cannabinoid agonists affect firing rates of neurons in the LC (Mendiguren and Pineda, 2006; Muntoni et al., 2006). Further, the cannabinoid agonist WIN 55,212-2 increases c-fos expression in the LC (Patel and Hillard, 2003) and increases forebrain NE release as well as increase indices of noradrenergic activity (Oropeza et al., 2005; Page et al., 2007; Page et al., 2008). In addition to possibly acting on brain stem noradrenergic projection neurons, endocannabinoids could also be acting within the BNST. CB1 receptors have been localized on presynaptic excitatory and inhibitory synaptic terminals within the BNST (Puente et al., 2010) and mRNA for CB1 receptors has been found in both projection neurons to the BNST as well as in intrinsic inhibitory neurons (Matsuda et al., 1993). The CB1 receptors within the BNST have been linked anatomically and functionally to reward pathways (Massi et al., 2008; Grueter et al., 2006).

Alternative hypotheses regarding the interaction of cannabinergic and noradrenergic systems are also possible. For example, activation of CB1 receptors on GABAergic terminals could suppress inhibition of neurons downstream from NE release in the BNST.

The hypothesis that the ECS may serve as a link between stress and noradrenergic dependent processes has also been proposed for the consolidation of aversive memories. It is known that noradrenergic transmission within the basolateral amygdala is critical for stress-induced enhancement of memory consolidation (Roozendaal et al., 2002; Roozendaal et al., 2004; Roozendaal et al., 2006). Campolongo et al., (2009) have found that cannabinoid antagonists impair and cannabinoid agonists enhance stress-induced memory consolidation and have proposed that stress may act to enhance memory, at least in part, by stimulating the release of endocannabinoids which then lead to the release of NE.

Although the results of this study support a possible interaction between the ECS and noradrenergic systems in stress-induced reinstatement of cocaine seeking behavior, blockade of swim stress-induced reinstatement by AM-251 may also reflect the interaction of the ECS with other brain pathways and neurotransmitters. For example, the ECS has been implicated in the regulation of stress response by the hypothalamic-pituitary-adrenal axis, as well as the release of numerous neurotransmitter systems involved in addiction, including GABA, glutamate, dopamine, serotonin, acetylcholine and neuropeptides (Lopez-Moreno). The interaction of the ECS with these systems in stress-induced reinstatement remains to be investigated.

We found that a cannabinoid antagonist blocks stress- but not cocaine-induced reinstatement of cocaine seeking behavior in mice. Further, we have found that non-reinstating dose of a cannabinoid agonist and a non-reinstating dose of an alpha-2 adrenergic autoreceptor antagonist synergize to produce reinstatement. These results are consistent with the hypothesis that stress exposure but not cocaine triggers the endogenous activation of CB1 receptors and that the ECS interacts with noradrenergic mechanisms to influence stress-induced reinstatement of cocaine-seeking behavior.

Acknowledgments

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Abbreviations

NE	norepinephrine
LC	locus coeruleus
BNST	bed nucleus of the stria terminalis
RM	repeated measures
FS	forced swim
ECS	endocannabinoid system

Highlights

Endocannabinoids and stress-induced cocaine reinstatement

Cannabinoid antagonist AM-251 blocks stress- induced cocaine reinstatement

Cannabinoid antagonist AM-251 does not block cocaine-induced cocaine reinstatement

Cannabinoid agonist does not induce cocaine reinstatement

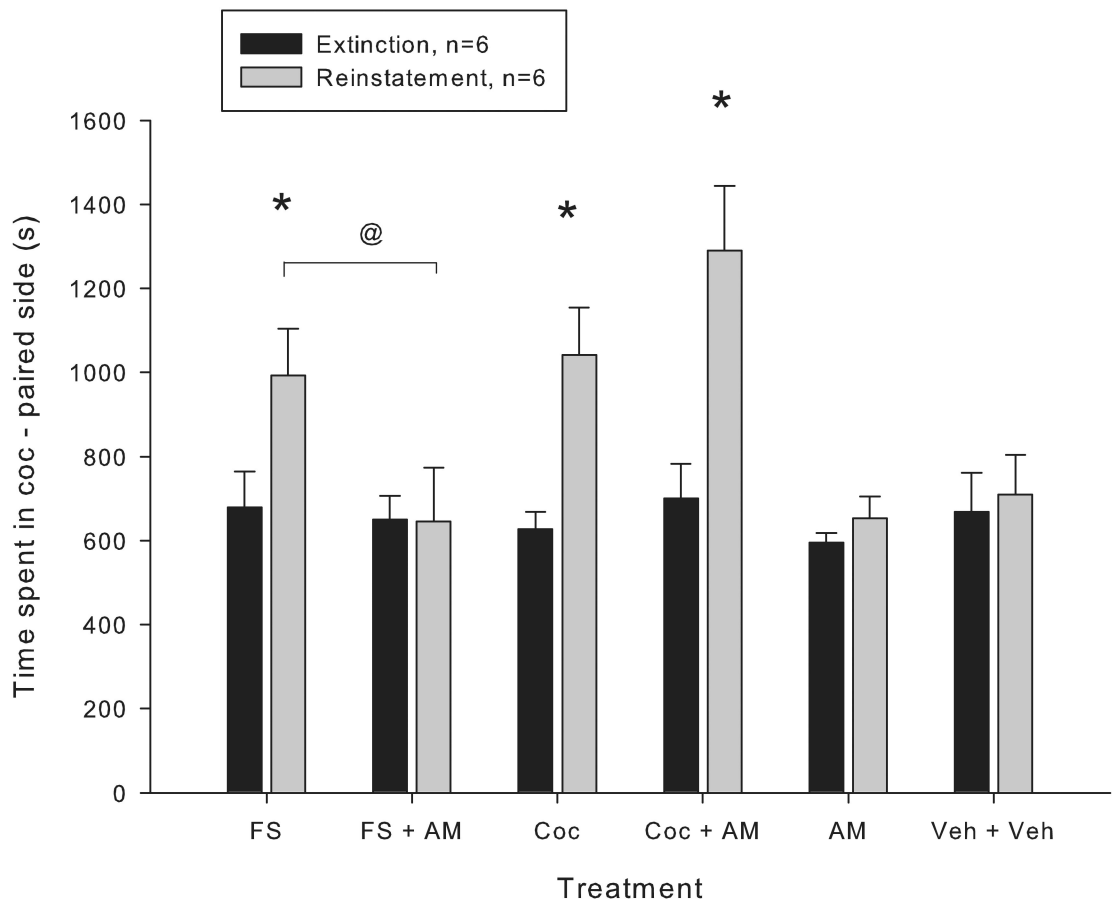Cannabinoid and noradrenergic agents synergize to induce cocaine reinstatement

Figure 1.
The effect of the cannabinoid antagonist AM-251 on forced swim- and cocaine-induced reinstatement. Data represent the time spent in the cocaine-paired compartment (mean +/- SEM) during the extinction session prior to reinstatement testing and after reinstatement testing with forced swim (6 minutes) + vehicle (FS), FS + AM-251(3 mg/kg, i.p.) (FS+AM), cocaine (15 mg/kg, i.p) + vehicle (Coc), cocaine + AM-251 (Coc+AM), vehicle, or AM-251. Vehicle and AM-251 were injected 30 minutes prior to reinstatement testing. Coc and FS were administered immediately prior to reinstatement testing. A significant increase in the time spent in the cocaine-paired compartment during reinstatement testing compared to the preceding extinction session was seen after both FS and cocaine (* =p<0.05, Holm-Sidak multiple comparison test) but not after AM-251 or vehicle alone. A significant difference between the time spent in the cocaine-paired compartment on reinstatement days was seen between the FS and FS+AM251 treatment groups (@ = p<0.05, Holm-Sidak multiple comparison test) but not between the Coc and the Coc + AM-251 groups.
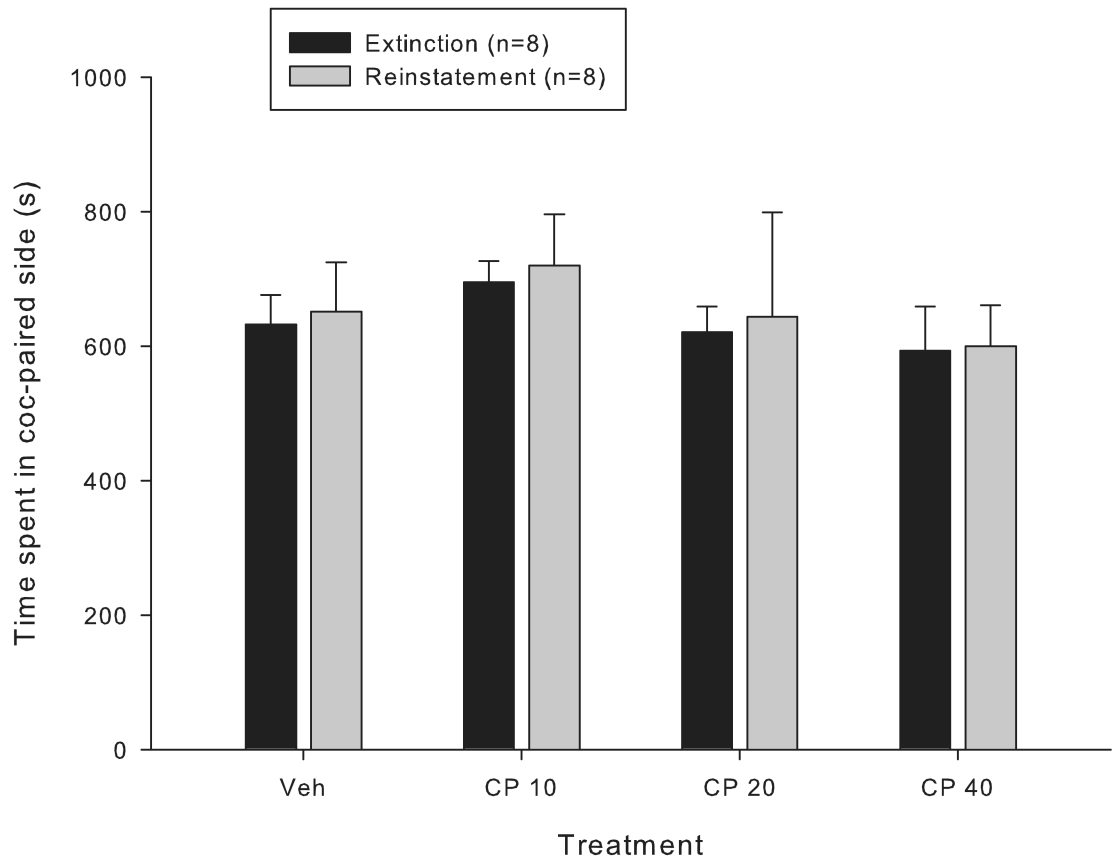
Figure 2.
The effect of the cannabinoid agonist CP 55,940 on reinstatement of extinguished cocaine-induced conditioned place preference. Data represent the time spent in the cocaine-paired compartment (mean +/- SEM) during the extinction session prior to reinstatement testing and after reinstatement testing with vehicle (Veh) or 10, 20 or 40 µg/kg, i.p. CP-55,940, 30 min prior to testing. There were no significant differences (two way RM ANOVA).
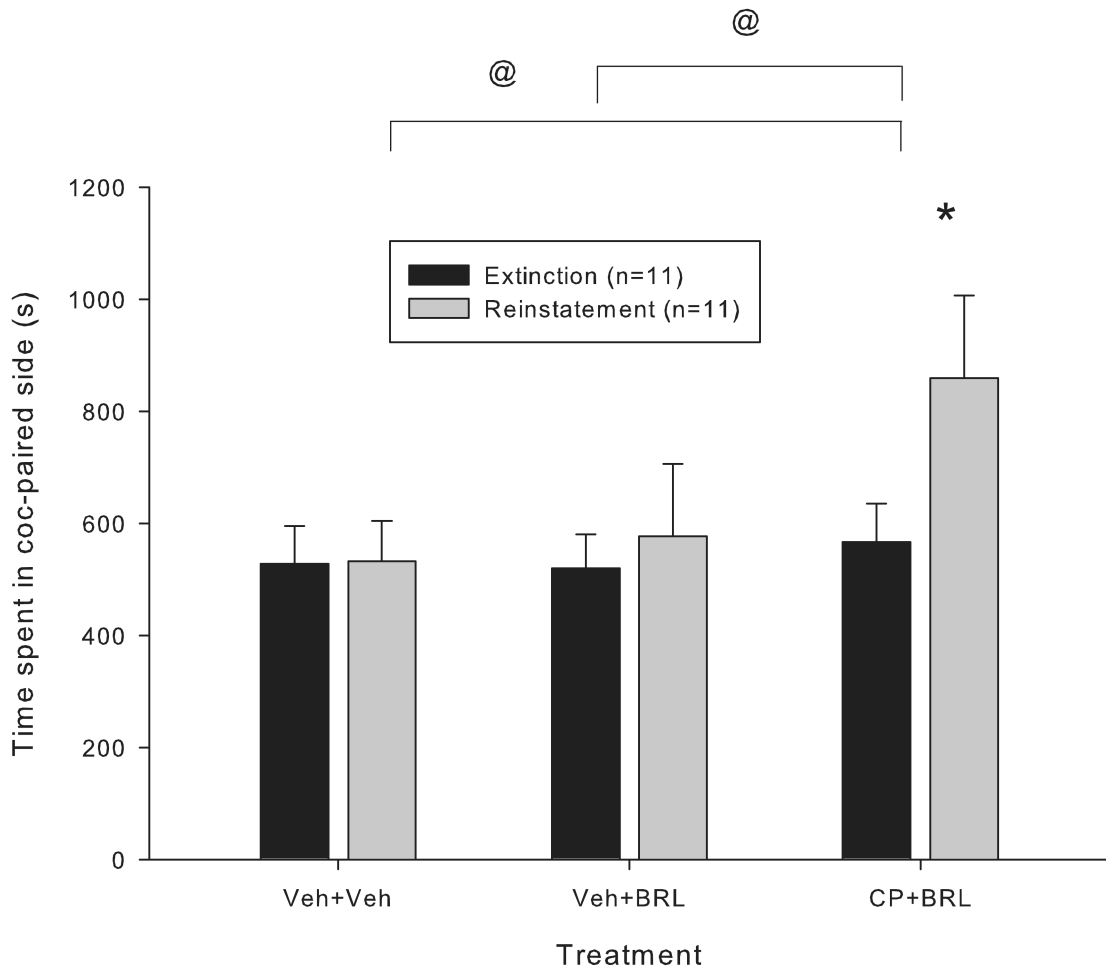
Figure 3.
The effect of combined administration of subthreshold doses of the cannabinoid agonist CP-55,940 and the alpha-2 adrenergic antagonist BRL-44408 on reinstatement of extinguished cocaine-induced conditioned place preference. Data represent the time spent in the cocaine-paired compartment (mean +/- SEM) during the extinction session prior to reinstatement testing and after reinstatement testing with vehicles (Veh + Veh), BRL-44408 (5 mg/kg, i.p.) and vehicle (BRL+ Veh), and BRL-44408 and CP 55,940 (20 μg/kg, i.p.) (CP+BRL). All injections were administered 30 min prior to reinstatement testing. A significant increase in the time spent in the cocaine-paired compartment during reinstatement testing compared to the preceding extinction session was seen after administration of CP and BRL (* =p<0.05, Holm-Sidak multiple comparison test) but not after BRL or vehicle alone. A significant difference between the time spent in the cocaine-paired compartment on reinstatement days was seen between the CP+BRL and the BRL +Veh and the Veh+Veh treatment groups (@ = p<0.05, Holm-Sidak multiple comparison test).