Pharmacology, Biochemistry and Behavior 96 (2010) 496–500

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Reducing endocannabinoid metabolism with the fatty acid amide hydrolase inhibitor, URB597, fails to modify reinstatement of morphine-induced conditioned floor preference and naloxone-precipitated morphine withdrawal-induced conditioned floor avoidance

Amanda L. McCallum, Cheryl L. Limebeer, Linda A. Parker *

Dept. of Psychology, University of Guelph, Guelph, Ontario, Canada N1G 2W1

ARTICLE INFO

Article history:
Received 6 April 2010
Received in revised form 9 July 2010
Accepted 15 July 2010
Available online 17 July 2010

Keywords:
URB597
Anandamide
Place preference
Place avoidance
Morphine withdrawal
Extinction
Reinstatement
Addiction
Post-traumatic stress disorder

ABSTRACT

The potential of the fatty acid amide hydrolase (FAAH) inhibitor, URB597, to modify drug prime-induced reinstatement of morphine-induced conditioned floor preference or naloxone-precipitated morphine withdrawal-induced conditioned floor avoidance was evaluated. In Experiment 1, morphine-induced conditioned floor preference was established across 4 conditioning trials. Following extinction training (4 trials), rats were pretreated with URB597 or vehicle prior to a morphine prime or a saline prime. Morphine reinstated the previously extinguished floor preference, but URB597 did not modify the strength of the reinstated preference. In Experiment 2, naloxone-precipitated morphine withdrawal-induced conditioned floor avoidance was established across 2 conditioning trials. Following extinction training (14 trials), rats were pretreated with URB597 or vehicle prior to a saline prime or a morphine withdrawal prime. The morphine withdrawal prime reinstated the previously extinguished floor avoidance, but URB597 did not modify the strength of reinstated avoidance. These results suggest that under the conditions in which URB597 promotes extinction (e.g., Manwell et al. (2009)) it does not interfere with drug-induced reinstatement of either conditioned floor preference or avoidance. That is, although activation of the endocannabinoid (eCB) system promotes extinction of aversive learning, it may not prevent reinstatement of that aversion by re-exposure to the aversive treatment.

1. Introduction

The endogenous cannabinoid (eCB) system has been implicated in extinction of previously learned aversive behaviors (Marsicano et al., 2002). Marsicano et al. (2002) initially reported that CB_1 receptor knockout mice and wild-type mice administered the CB_1 inverse agonist/antagonist, Rimonabant (SR141716), showed impaired extinction in classical auditory fear-conditioning tests, with memory acquisition and consolidation remaining unaffected. Using the aversively motivated Morris water maze task, Varvel and Lichtman (2002) reported that CB_1 knockout mice and wild-type mice showed similar acquisition rates in learning to swim to a fixed platform; however, the CB_1 deficient mice demonstrated deficits during a subsequent reversal task in which the mice were required to inhibit their previously learned behavior. On the other hand, CB_1 agonists have been reported to enhance the rate of extinction of aversively motivated tasks (Chhatwal et al., 2005; Pamplona et al., 2006). These effects on extinction are selective to aversive memories (e.g., Lutz, 2007), but not those produced by rewarding stimuli (Harloe et al., 2008; Holter et al., 2005).

Of most interest to the current study, Manwell et al. (2009) found that pretreatment with a fatty acid amide hydrolase (FAAH) inhibitor, URB597, selectively enhanced extinction of a conditioned floor avoidance produced by a naloxone-precipitated morphine withdrawal (see Azar et al., 2003; Parker and Joshi, 1998), but not a conditioned floor preference produced by morphine. By deactivating FAAH, URB597 selectively prolongs the duration of action of the eCB, anandamide, at the sites at which it is produced 'on demand.' The ID_{50} for FAAH inhibition by URB597 in rats ex vivo is 0.15 mg/kg ip (Kathuria et al., 2003; Fegley et al., 2005). At the dose (0.3 mg/kg) employed by Manwell et al. (2009), URB597 produces maximal inhibition of FAAH within 15 min of administration and persists for at least 16 h (Fegley et al., 2005). This effect is associated with a parallel increase in brain anandamide content which attained peak levels 1 to 6 h following the injection. Furthermore, at the dose of 0.3 mg/kg, URB597 produces maximal efficacy in anyxiolytic-like (Kathuria et al., 2003; Patel and Hillard, 2006; Scherma et al., 2008a), anti-depressant-like (Gobbi et al., 2005) and anti-nausea-like effects (Cross-Mellor et al., 2007; Rock et al., 2008) in rats. The enhanced extinction of the floor avoidance was most likely produced by action of anandamide on

* Corresponding author. Tel.: +1 519 824 4120, 56330; fax: +1 519 837 8629.
E-mail address: parkerl@uoguelph.ca (L.A. Parker).

0091-3057/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2010.07.010

the CB_1 receptor, because Rimonabant prolonged the duration of extinction relative to vehicle controls (Manwell et al., 2009).

Although URB597 facilitated extinction of conditioned floor avoidance, this facilitated extinction did not prevent the potential of a subsequent prime of naloxone-precipitated morphine withdrawal to reinstate the previously extinguished floor avoidance (Manwell et al., 2009). Such drug-induced reinstatement effects provide evidence that extinction is not unlearning (Bouton, 2002), but instead new inhibitory learning. These results suggest that eCB system manipulation by means of FAAH inhibition during extinction does not result in an elimination of the aversive memories given that they can be reinstated. However, it is not known under these conditions whether URB597 given prior to the actual reinstatement trial will result in attenuation of the reinstated aversive memory, as it has previously been reported to prevent reinstatement of a nicotine-induced conditioned place preference (Scherma et al., 2008b). It is conceivable that elevated levels of anandamide at the time of reinstatement of either a morphine-induced floor preference or a morphine withdrawal-induced floor avoidance would suppress the reinstated memory. Therefore, the present study was designed to evaluate the potential of URB597, at the maximally effective dose reported in other studies (Forget et al., 2009; Manwell et al., 2009; Scherma et al., 2008b) administered during reinstatement testing to interfere with reinstatement of both a previously extinguished morphine-induced floor preference [Experiment 1] and a naloxone-precipitated morphine withdrawal-induced conditioned floor avoidance [Experiment 2].

2. Materials and method

2.1. Subjects

The subjects in Experiment 1 and 2 were male Sprague–Dawley rats. The animals were maintained on an *ad libitum* schedule of food and water and were pair-housed in shoebox cages in the colony room at an ambient temperature of 21 degrees Celsius with a 12 h/12 h reverse light/dark schedule (lights off at 7:00 h). Experimental procedures began at least 3 h after the beginning of the dark cycle and were completed within 2 h prior to the end of the dark cycle. All procedures adhered to the guidelines of the Canadian Council of Animal Care and were approved by the Animal Care Committee of the University of Guelph.

2.2. Drugs

Morphine was prepared in physiological saline at concentrations of either 10 mg/ml [Experiment 1] or 20 mg/ml [Experiment 2] and administered subcutaneously (sc) in a volume of 1 ml/kg at 10 min prior to conditioning [Experiment 1] or 4 h before conditioning [Experiment 2]. Naloxone was prepared in physiological saline in a concentration of 1 mg/ml and administered (sc) in a volume of 1 ml/kg at 10 min prior to conditioning. URB597 (Cayman Chemicals) was prepared in 2-hydroxypropyl-ß-cyclodextrin (2-HPBCD, 45%) at a concentration of 0.3 mg/kg (ip) 2 h prior to reinstatement. At a dose of 0.3 mg/kg, URB-597 has been shown to produce a slow and consistent accumulation of anandamide in the brain with maximal effect occurring 2 h post injection (Fegley et al., 2005).

2.3. Apparatus

The conditioning apparatus used was a black Plexiglas rectangular box (60×25×25 cm) with a wire-mesh lid (as previously described in Manwell et al., 2009). During conditioning trials, the tactile cues on both sides of the box were identical. However, during pretest and choice tests, one side of the chamber had a metal hole floor and the other side had a metal grid floor (counterbalanced orientation), and the intersection of the two floors was defined as a neutral zone (9×25 cm) which was not included in the analysis. The amount of time (seconds) each rat spent on each of the floors was recorded and later analyzed by the Noldus Ethovision activity monitoring system (Noldus Information Technology, Sterling, VA.) Pretests did not reveal a significant difference between time spent on the hole or grid floors demonstrating that the apparatus provides an unbiased test of conditioned preference and aversion.

2.4. Procedure

2.4.1. Experiment 1: effect of URB-597 on reinstatement of morphine-induced conditioned preference

A 10-min pretest was administered and the amount of time spent on each floor was measured. The rats were subsequently assigned to groups matched on the basis of their pretest score. The rats received 4 conditioning trials. During conditioning cycles all rats were injected with morphine or saline 10 min before placement in the box with a distinctive floor for 20 min. Therefore, each conditioning cycle was comprised of one morphine trial and one saline trial separated by 24 h. Additionally, each of the cycles was separated by 48–72 h. The order of the morphine trial within a cycle and the floor paired with morphine were counterbalanced among rats. Forty-eight hours after the 4th conditioning cycle, the rats were given a 10-min test. Starting 24 h after the test, the rats were given repeated 10-min extinction choice test trials, each separated by 24 h. The trials continued until there was no significant difference in preference for the morphine-paired floor and the saline-paired floor on at least 2 trials. One week subsequent to the final extinction trial, the rats received a reinstatement cycle. They were assigned-matched for drug-paired floor and order of morphine trial during conditioning, to group URB597 ($n=12$) and VEH ($n=11$). On each of the next two trials the rats were injected (ip) with either Vehicle (VEH) or 0.3 mg/kg URB597 at 2 h prior to a 10-min test trial. Ten minutes prior to one reinstatement test trial the rats were injected (sc) with saline (saline reinstatement trial), and 10 min prior to the other test trial (24 h later), the rats were injected (sc) with 5 mg/kg of morphine (morphine reinstatement trial). The order of morphine and saline trials were counterbalanced.

2.4.2. Experiment 2: effect of URB-597 on reinstatement of naloxone-precipitated morphine withdrawal-induced conditioned avoidance

The assignment of rats to groups was matched according to the results of a 10-min pretest. They were then given 2 conditioning trial cycles (separated by 72 h), each comprised of a 2-day schedule separated by 24 h. For each conditioning cycle, on Day 1 the rats were injected with saline (sc) 10 min before being placed in the conditioning box with distinctive floor for 20 min. On Day 2, rats were administered 20 mg/kg of morphine (sc) at 4 h, and 1 mg/kg of naloxone (sc) at 10 min before placement in the conditioning box with the opposite distinctive floor (as on Day 1) for 20 min (see Azar et al., 2003). Extinction trials began 72 h after the final conditioning cycle. On each trial, the rats received drug-free access to both floors for 10 min. The trials occurred every 24 h for 14 days until there was no longer a significant difference between the morphine withdrawal-paired floor and saline-paired floor for two consecutive days.

A reinstatement cycle commenced one week after the final extinction trial. On Day 1 rats were injected (ip) with either VEH ($n=12$) or 0.3 mg/kg URB597 ($n=12$), and then with 1 ml/kg saline (sc) 10 min prior to a 10-min choice test. On Day 2, the rats were administered 10 mg/kg of morphine (sc) at 2 h prior to an injection (ip) of 0.3 mg/kg URB597 or VEH. Two hours later they all received an injection (sc) of naloxone (0.5 mg/kg) 10 min prior to a 10-min reinstatement choice test. The mean amount of time spent on each floor and the overall distance (cm) traveled in the conditioning chamber was analyzed by the Noldus Ethovision activity monitoring system.

2.5. Data analysis

To determine the effect of conditioning, in both Experiments 1 and 2, the mean seconds spent on the treatment-paired and saline-paired floors on the pretest and first extinction test trial were compared using a 2 by 2 repeated measures ANOVA. Extinction was defined as a non-significant difference ($p>.05$) in the time spent on the treatment-paired floor and on the saline-paired floor for at least 2 consecutive extinction trials, as assessed by planned paired t-tests.

For the reinstatement trials of both Experiments 1 and 2, the mean seconds spent on the treatment-paired floor and saline-paired floor was entered into a mixed factors ANOVA with the between groups factor of reinstatement pretreatment (URB597 or VEH) and the within groups factors of floor (Experiment 1: morphine-paired floor, saline-paired floor; Experiment 2: morphine withdrawal-paired floor, saline-paired floor) and reinstatement trial (Experiment 1: saline prime, morphine prime; Experiment 2: saline prime, morphine withdrawal prime). As well, to determine the effect of the reinstatement treatment on activity during each reinstatement trial, the overall distance traveled (cm) by each rat was entered into a mixed factor ANOVA with the factors of reinstatement pretreatment (URB597 or VEH) and reinstatement trial (Experiment 1: saline prime, morphine prime; Experiment 2: saline prime, morphine withdrawal prime). Significance levels were set at $p<.05$.

3. Results

3.1. Experiment 1: effect of URB-597 on reinstatement of morphine-induced conditioned preference

3.1.1. Extinction trials

Morphine produced a conditioned floor preference that extinguished following a single test trial. Fig. 1 presents the mean (±SEM) number of seconds that the rats spent on the morphine- and saline-paired floors during the pretest and on each extinction trial. The 2 by 2 repeated measures ANOVA for the pretest and first extinction test trial revealed a significant floor by trial interaction, $F(1,22)=8.6$; $p<.01$. Although the rats did not differ in floor preference on the pretest, they spent more time on the morphine-paired floor than the saline-paired floor on the first test trial, $t(22)=3.4$; $p<.01$. There were no significant floor preferences on any other trial.

3.1.2. Reinstatement trials

The morphine prime reinstated the conditioned floor preference, however pretreatment with URB597 did not modify this reinstatement effect. Fig. 2 presents the mean (±SEM) seconds spent on the morphine- and saline-paired floor for both URB597 and vehicle pretreated groups during the saline reinstatement trial (top half) and the morphine reinstatement trial (bottom half). The 2 by 2 by 2 mixed factors ANOVA revealed only a significant floor by reinstatement trial effect, $F(1, 21)=8.4$; $p<.01$. There was a significant effect of conditioning floor on the morphine-primed trial, $F(1, 21)=5.2$; $p<.05$, but not on the saline-primed trial, but URB597 did not modify the strength of the floor preference reinstated by the morphine prime.

Pretreatment with URB597 did not modify the overall activity level of the rats (data not depicted). The $2\times2\times2$ mixed factors ANOVA of the distance traveled during the reinstatement trials revealed no significant effects.

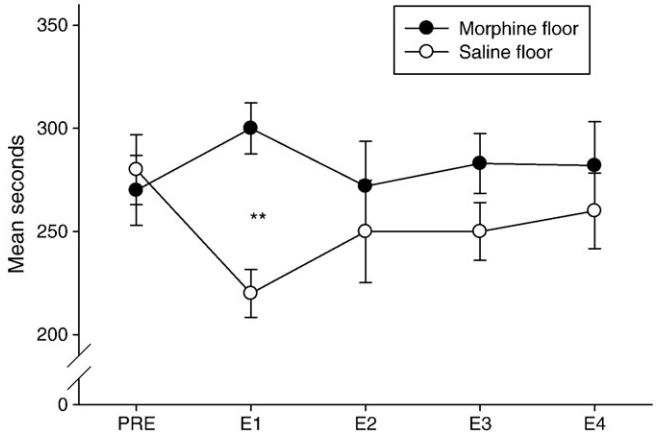

Fig. 1. Mean (±SEM) seconds spent on the morphine-paired floor and on the saline-paired floor during the pretest and each of the 4 extinction test trials in Experiment 1 (** = $p<.01$).

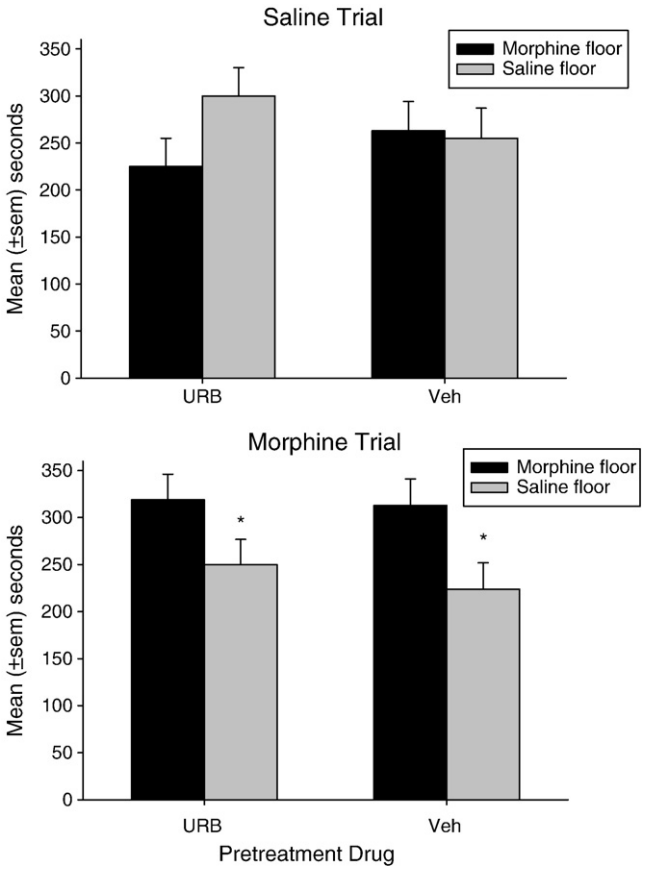

Fig. 2. Mean (±SEM) seconds spent on the morphine-paired floor and the saline-paired floor during the saline (upper half) and morphine (lower half) reinstatement tests for rats that had been pretreated with URB-597 or VEH just prior to reinstatement in Experiment 1 (* = $p<.05$).

3.2. Experiment 2: effect of URB-597 on reinstatement of naloxone-precipitated morphine withdrawal-induced conditioned avoidance

3.2.1. Extinction trials

Naloxone-precipitated morphine withdrawal produced a conditioned floor avoidance that persisted across 12 extinction trials. Fig. 3 presents the mean (±SEM) number of seconds that the rats spent on the withdrawal- and saline-paired floors during the pretest and each daily extinction test trial. The 2×2 repeated measures ANOVA for the pretest and the first extinction test trial revealed a significant floor by trial interaction, $F(1, 23)=7.3$; $p<.01$; the rats avoided the withdrawal-paired floor on the first extinction test trial, $t(23)=3.1$; $p<.01$, but not on the pretest. As well, on trials, 2, 3, 5, 8, 9–12 (but not on trials 13 and 14) the rats spent significantly less time on the withdrawal-paired floor than the saline-paired floor, *ts* $(23)>2.1$; *ps* $<.05$.

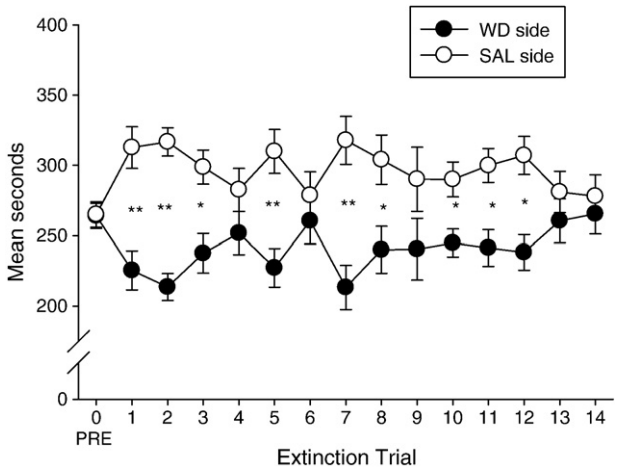

Fig. 3. Mean (±SEM) seconds spent on the naloxone-precipitated morphine withdrawal-paired floor and on the saline-paired floor during the pretest and each of the 14 extinction test trials in Experiment 2 (* = $p<.05$; ** = $p<.01$).

3.2.2. Reinstatement trials

Naloxone-precipitated morphine withdrawal reinstated the extinguished floor avoidance and URB597 did not interfere with this reinstatement effect. Fig. 4 presents the mean (±SEM) number of seconds that the rats spent on the morphine withdrawal- and saline-paired floors for both the URB597 and vehicle pretreated groups on the saline reinstatement trial (top half) and on the naloxone-precipitated morphine withdrawal reinstatement trial (bottom half). The 2×2×2 mixed factors ANOVA revealed a significant reinstatement drug prime effect, $F(1, 22) = 15.8$; $p<.01$, conditioning floor effect, $F(1, 22) = 11.4$; $p<.01$ and a significant floor by reinstatement trial effect, $F(1, 22) = 8.9$; $p<.01$. On the morphine withdrawal reinstatement trial, but not on the saline-primed trial, there was a significant effect of conditioning floor, $F(1, 22) = 14.0$; $p<.001$. The rats spent less time on the floor previously associated with naloxone-precipitated morphine withdrawal, but there was no effect of pretreatment with either the URB597 or vehicle on the strength of that place avoidance.

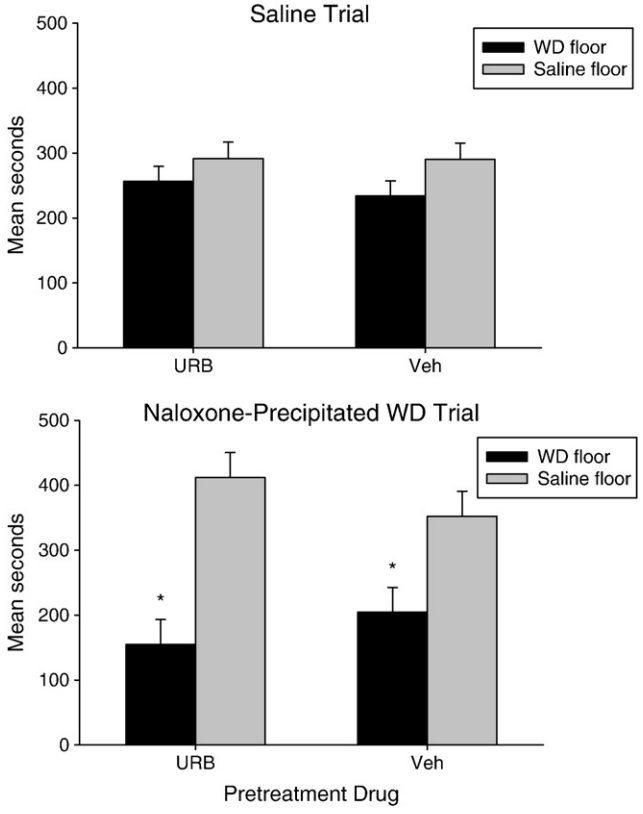

Fig. 4. Mean (±SEM) seconds spent on the naloxone-precipitated morphine withdrawal-paired floor and the saline-paired floor during the saline (upper half) and naloxone-precipitated morphine withdrawal (lower half) reinstatement test for rats that had been pretreated with URB-597 or VEH 2 h prior to the reinstatement test in Experiment 2 (* = $p<.05$).

Pretreatment with URB597 did not modify the overall activity of the rats during the reinstatement trials (data not depicted). The 2×2 mixed factors ANOVA of distance traveled on each trial revealed only a significant effect of reinstatement trial, $F(1, 22) = 91.0$; $p<.01$; rats were less active overall following the naloxone-precipitated morphine withdrawal prime than the saline prime, but URB597 did not modify the level of activity on either trial.

4. Discussion

Morphine produced a conditioned floor preference (Experiment 1) and naloxone-precipitated morphine withdrawal produced conditioned floor avoidance (Experiment 2). Consistent with the literature, the floor preference extinguished rapidly, but the floor avoidance was highly resistant to extinction (Manwell et al., 2009; Parker and McDonald, 2000). Extinction did not eliminate the learned preference or avoidance, because a morphine prime (Experiment 1) or a naloxone-precipitated morphine withdrawal prime (Experiment 2) reinstated the floor preference or avoidance, respectively. However, at a dose (0.3 mg/kg) that produces maximal inhibition of FAAH for up to 16 h (Fegley et al., 2005), URB597 pretreatment did not modify the strength of the reinstated preference or avoidance.

These results extend the findings of Manwell et al. (2009) who reported that although URB597administered prior to each extinction trial facilitated extinction of conditioned floor avoidance, this facilitated extinction was not translated into impaired drug-induced reinstatement of the avoidance. That is, prolonged action of anandamide by URB597 enhances extinction of aversive learning (Manwell et al., 2009); however whether it is administered during extinction training (Manwell et al., 2009) or during reinstatement training (Experiment 2 here), URB597 did not prevent drug-induced reinstatement of the conditioned floor avoidance.

Although URB597 did not attenuate reinstatement of a morphine-induced conditioned floor preference or a naloxone-precipitated morphine withdrawal-induced conditioned floor avoidance in the present study, it has recently been reported to attenuate drug prime-induced reinstatement of a previously extinguished nicotine-induced conditioned place preference (Scherma et al., 2008b) as well as nicotine-induced self-administration (Forget et al., 2009) at the same dose (0.3 mg/kg) administered in the present study. This is somewhat surprising, because the same group also reported that the CB_1 inverse agonist/antagonist, rimonabant, also interfered with nicotine-induced reinstatement (Forget et al., 2009). Consistent with the reports of the present study, Cippitelli et al. (2008) have recently reported that URB597 has no effect on reinstatement of previously extinguished alcohol self-administration produced by footshock or by yohimbine. Furthermore, the anandamide reuptake inhibitor, AM404, also failed to modify reinstatement of previously extinguished alcohol self-administration by an alcohol prime (Cippitelli et al., 2007). Therefore, at present, it appears that the potential of FAAH inhibition to interfere with reinstatement of drug seeking may be drug-dependent.

FAAH inhibitors magnify and prolong the action of anandamide at the CB_1 receptor only when and where it is synthesized and released on demand. On the other hand, systemic delivery of direct agonists or antagonists affects CB_1 receptors throughout the brain. Considerable evidence indicates that the CB_1 antagonist/inverse agonist, Rimonabant, interferes with reinstatement of cannabinoid, cocaine, heroin and methamphetamine induced reinstatement of self-administration (e.g., Fattore et al., 2007, for review); however, we are unaware of any

reports of the effect of direct agonists on reinstatement of previously extinguished self-administration or conditioned place preference produced by a priming dose of the conditioning drug.

The potential of FAAH inhibition to promote extinction of conditioned floor avoidance (Manwell et al., 2009), but not to interfere with subsequent reinstatement of that learned avoidance suggests that activation of the eCB system is important for the inhibition of aversive memories, but these memories can be reinstated by triggers that initially created them (naloxone-precipitated morphine withdrawal). The eCB system appears to be important in the inhibition of aversive memories, but may not be critical for the elimination of these memories.

Acknowledgements

We would like to thank Eric Hutchinson for assistance with data collection. This research was supported by a research grant to Linda A. Parker from the Natural Sciences and Engineering Research Council of Canada. Please address all reprint requests to: parkerl@uoguelph.ca.

References

Azar MR, Jones BC, Schulteis G. Conditioned place aversion is a highly sensitive index of acute opioid dependence and withdrawal. Psychopharmacology 2003;170:42–50.
Bouton ME. Context, ambiguity, and unlearning: sources of relapse after behavioral extinction. Biol Psychiatry 2002;52:976–86.
Chhatwal JP, Davis M, Maguschak KA, Ressler KJ. Enhancing cannabinoid neurotransmission augments the extinction of conditioned fear. Neuropsychopharmacology 2005;30:516–24.
Cippitelli A, Cannella N, Braconi S, Duranti A, Tontini A, Bilbao A, et al. Increase of brain endocannabinoid anandamide levels by FAAH inhibition and alcohol abuse behaviours in the rat. Psychopharmacology 2008;198:449–60.
Cippitelli A, Bilbao A, Gorriti MA, Navarro M, Massi M, Piomelli D, et al. The anandamide transport inhibitor AM404 reduces ethanol self-administration. Eur J Neurosci 2007;26:476–86.
Cross-Mellor SK, Ossenkopp KP, Piomelli D, Parker LA. Effects of the FAAH inhibitor, URB597, and anandamide on lithium-induced taste reactivity responses: a measure of nausea in the rat. Psychopharmacology 2007;190:135–43.
Fattore L, Spano MS, Deiana S, Melis V, Cossu G, Fadda P, et al. An endocannabinoid mechanism in relapse to drug seeking: a review of animal studies and clinical perspectives. Brain Res Rev 2007;53:1-16.
Fegley D, Gaetani S, Duranti A, Tontini A, Mor M, Tarzia G, et al. Characterization of the fatty acid amide hydrolase inhibitor cyclohexyl carbamic acid 3′-carbamoyl-biphenyl-3-yl ester (URB-597): effects on anandamide and oleoylethanolamide deactivation. J Pharmacol Exp Ther 2005;313:352–8.
Forget B, Coen KM, Le Foll B. Inhibition of fatty acid amide hydrolase reduces reinstatement of nicotine seeking but not break point for nicotine self-administration: comparison with CB1 receptor blockade. Psychopharmacology 2009;205:613–24.
Gobbi G, Bambico FR, Mangieri R, Bortolato M, Campolongo P, et al. Antidepressant-like activity and modulation of brain monoamergic transmission by blockade of anandamide hydrolysis. Proc Natl Acad Sci USA 2005;102:18620–6.
Harloe J, Thorpe A, Lichtman AH. Differential endocannabinoid regulation of extinction in appetitive and aversive Barnes maze tasks. Learn Mem 2008;15:806–9.
Holter SM, Kallnik M, Wurst W, Mariscano G, Lutz B, Wotjak CT. Cannabinoid CB1 receptor is dispensable for memory extinction in an appetitively-motivated learning task. Eur J Pharmacol 2005;510:69–74.
Kathuria S, Gaetani S, Fegley D, Valino F, Duranti A, Tontini A, et al. Modulation of anxiety through blockade of anandamide hydrolysis. Nat Med 2003;9:76–81.
Lutz B. The endocannabinoid system and extinction learning. Mol Neurobiol 2007;36: 92-101.
Manwell LA, Satvat E, Lang ST, Allen CP, Leri F, Parker LA. FAAH inhibitor, URB-597, promotes extinction and CB1 antagonist, SR141716, inhibits extinction of conditioned aversion produced by naloxone-precipitated morphine withdrawal, but not extinction of conditioned preference produced by morphine in rats. Pharmacol Biochem Behav 2009;94:154–62.
Marsicano G, Wotjak CT, Azad SC, Bisogno T, Rammes G, Cascio MG, et al. The endogenous cannabinoid system controls extinction of aversive memories. Nature 2002;418:530–4.
Pamplona FA, Prediger RD, Pandolfo P, Takahashi RN. The cannabinoid receptor agonist WIN 55,212-2 facilitates the extinction of contextual fear memory and spatial memory in rats. Psychopharmacology 2006;188:641–9.
Parker LA, Joshi A. Naloxone-precipitated morphine withdrawal induced place aversions: effect of naloxone at 24 hours post morphine. Pharmacol Biochem Behav 1998;72: 87–92.
Parker LA, McDonald. Reinstatement of both a conditioned place preference and conditioned place aversion with drug primes. Pharmacol Biochem Behav 2000;66: 559–61.
Patel S, Hillard CJ. Pharmacological evaluation of cannabinoid receptor ligands in a mouse model of anxiety: further evidence for an anxiolytic role for endogenous cannabinoid signaling. J Pharmacol Exp Ther 2006;318:304–11.
Rock EM, Limebeer CL, Mechoulam R, Piomelli D, Parker LA. The effect of cannabidiol and URB597 on conditioned gaping (a model of nausea) elicited by a lithium-paired context in the rat. Psychopharmacology 2008;196:389–95.
Scherma M, Medalie J, Fratta W, Vadivel SK, Makriyannis A, et al. The endogenous cannabinoid anandamide has effects on motivation and anxiety that are revealed by fatty acid amide hydrolase (FAAH) inhibition. Neuropharmacology 2008a;54: 129–40.
Scherma M, Panlilio LV, Fadda P, Fattore L, Gamaleddin I, Le Foll B, et al. Inhibition of anandamide hydrolysis by cyclohexyl carbamic acid 3′-carbamoyl-3-yl ester (URB597) reverses abuse-related behavioral and neurochemical effects of nicotine in rats. J Pharmacol Exp Ther 2008b;327(2):482–90.
Varvel SA, Lichtman AH. Evaluation of CB1 receptor knockout mice in the Morris water maze. J Pharmacol Exp Ther 2002;301:915–24.