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Research report

Nociceptin receptor activation does not alter acquisition, expression, extinction and reinstatement of conditioned cocaine preference in mice

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ABSTRACT

Growing evidence indicates that targeting nociceptin receptor (NOP) signaling may have therapeutic efficacy in treating alcohol and opioid addiction. However, little is known about the therapeutic value of selective NOP agonists for the treatment of cocaine dependence. Recently, we identified a highly selective, brain-penetrant NOP small molecule agonist (SR-8993), and using this compound, we previously showed that nociceptin receptor activation attenuated consolidation of fear-related memories. Here, we sought to determine whether SR-8993 also affects the rewarding properties of cocaine. Using a conditioned place preference (CPP) procedure, we show that SR-8993 (3 or 10 mg/kg) failed to disrupt acquisition or expression of cocaine CPP (7.5 or 15 mg/kg) in C57BL/6 mice. Additionally, SR-8993 did not affect rate of extinction or reinstatement (yohimbine- and cocaine-induced) of cocaine CPP. These studies indicate that selective activation of NOP may not be sufficient in reducing behavioral responses to cocaine.

1. Introduction

Nociceptin (orphanin FQ, N/OFQ) is an endogenous 17 amino acid peptide that has high affinity for the nociceptin receptor (NOP; sometimes called opioid-like receptor 1) (Lachowicz et al., 1995; Meunier et al., 1995; Reinscheid et al., 1995). NOP has similar sequence homology to classical opioid receptors (mu, delta and kappa) and is classified as the fourth member of the opioid receptor family (Witkin et al., 2014), but classical opioid peptides do not bind to NOP (Reinscheid et al., 1995; Wollemann and Benyhe, 2004). Although originally studied in pain, nociceptin and NOP are anatomically located in an ideal position for reward processing, as they are distributed throughout reward- and stress-related brain regions such as medial prefrontal cortex, ventral tegmental area, nucleus accumbens, lateral hypothalamus, central amygdala and bed nucleus of stria terminalis (Neal et al., 1999a, 1999b). Recent animal studies have confirmed an important role for nociceptin and NOP in multiple aspects of addiction-related processes, making nociceptin an attractive target for the

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development of therapeutics for the management of drug dependence (Lambert, 2008; Zaveri, 2011; Witkin et al., 2014).

Several lines of evidence support a role for nociceptin in addiction-related processes. For example, when injected intracranially, nociceptin reduces drug-induced dopamine release and c-fos activation in the nucleus accumbens, key mechanisms involved in reward and motivation (Ciccocioppo et al., 2000; Di Giannuario and Pieretti, 2000; Lutfy et al., 2001). In behavioral studies, intracranial administration of nociceptin attenuates addiction-related responses to opioids (Murphy et al., 1999; Ciccocioppo et al., 2000), psychostimulants (Lutfy et al., 2002; Kotlinska et al., 2003; Zhao et al., 2003; Bebawy et al., 2010) and ethanol (Ciccocioppo et al., 1999; Martin-Fardon et al., 2000), and withdrawal symptoms induced by morphine (Kotlinska et al., 2000) and ethanol (Economidou et al., 2011; Aujla et al., 2013). More recently, using small molecule compounds, preclinical studies have revealed that NOP agonists attenuate addiction-related behaviors similarly to nociceptin (Shoblock et al., 2005; Economidou et al., 2006; Kuzmin et al., 2007; Toll et al., 2009), although some discordant result has been reported in cocaine studies (Kotlinska et al., 2002). The discrepancy between nociceptin and small molecule agonist data may be explained by some of the NOP agonists having affinity for other opioid receptors (Wichmann et al., 2000; Toll et al., 2009), thus making it difficult to rule out interaction with multiple receptors. Therefore, development of highly selective NOP ligands is needed to identify the clinical significance of NOP in the treatment of addiction.

Recently, SR-8993 was identified as a highly selective, brain-penetrable NOP agonist, and using this compound, Andero et al. (2013) showed that nociceptin attenuates consolidation of fear-related memories. Here, we sought to determine whether the same systemically active compound also affects cocaine conditioned behaviors. Using a conditioned place preference (CPP) procedure, we show that SR-8993 failed to disrupt acquisition, expression, extinction and reinstatement of cocaine CPP in mice. Thus, these studies indicate that selective activation of NOP with SR-8993 is not sufficient in reducing place conditioning effects of cocaine.

2. Results

2.1. *Effects of SR-8993 on acquisition of cocaine CPP*

SR-8993 (3 or 10 mg/kg) was injected 30 min or 2 h before each cocaine (7.5 or 15 mg/kg) conditioning session. For additional controls, some mice were conditioned with saline, and in other mice naloxone (NLX), which has been previously shown to attenuate acquisition of cocaine CPP (Kim et al., 1997), was used as a positive control. In mice conditioned with 15 mg/kg of cocaine and treated 30 min before conditioning (Fig. 1A), a one-way ANOVA revealed a significant main effect of group ($F_{4,33}=8.6$, $p<0.0001$). Cocaine conditioned mice treated with vehicle during acquisition showed robust CPP compared to saline condition animals (Newman–Keuls test, $p<0.001$ for saline cond. vs. vehicle), indicating that cocaine effectively elicited a CPP. Compared to vehicle, naloxone significantly reduced CPP, but SR-8993 had no effect (Newman–Keuls test, $p<0.05$ for vehicle vs. NLX, $p>0.05$ for vehicle vs. SR-8993 at 3 and 10 mg/kg). In mice conditioned with 15 mg/kg of cocaine and treated with SR-8993 (3 or 10 mg/kg) 2 h before conditioning (Fig. 1B), no significant main effect was observed ($F_{2,20}=1.4$, $p>0.05$). Similarly, in mice conditioned with 7.5 mg/kg of cocaine and treated with SR-8993 30 min (Fig. 1C) or 2 h (Fig. 1D) before conditioning, no significant

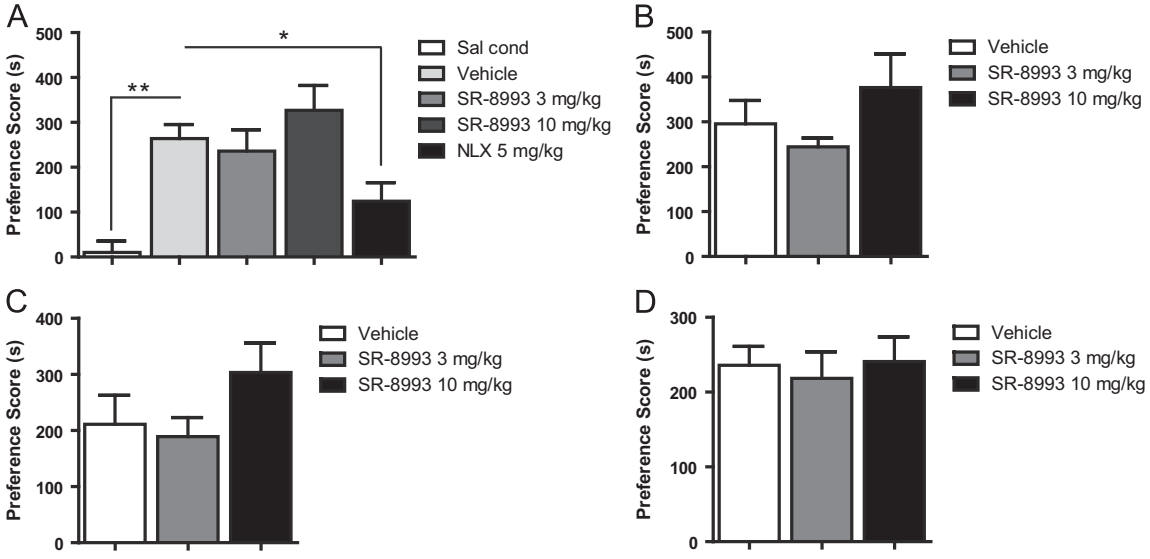

Fig. 1 – Effects of SR-8993 on acquistion of cocaine CPP. (A) Cocaine conditioned mice that received vehicle injections prior to each conditioning session showed robust CPP compared to saline conditioned mice. Naloxone significantly reduce cocaine CPP compared to vehicle. SR-8993 (3 mg/kg or 10 mg/kg) injections 30 min (A) or 2 h (B) before conditioning did not alter acquisition of CPP in mice conditioned with 15 mg/kg of cocaine. SR-8993 when injected (C) 30 min or (D) 2 h before conditioning did not change acquisition of CPP in mice conditioned with 7.5 mg/kg of cocaine. *$p<0.05$, **$p<0.001$ indicate a significant difference from vehicle via Newman–Keuls *post-hoc* test ($n=6$–9 per group). Data are mean ± SEM.

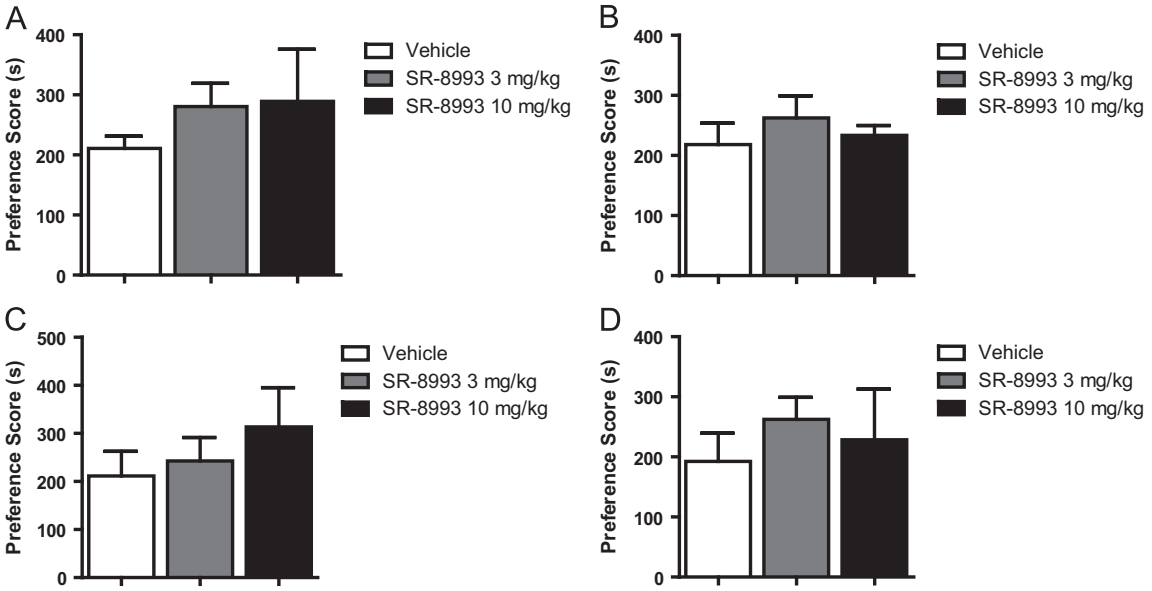

Fig. 2 – Effects of SR-8993 on expression of cocaine CPP. SR-8993 (3 mg/kg or 10 mg/kg) injection 30 min (A) or 2 h (B) before the expression test did not alter expression of CPP in mice conditioned with 15 mg/kg of cocaine, nor did SR-8993 injection (C) 30 min or (D) 2 h before the expression test change CPP scores in mice conditioned with 7.5 mg/kg of cocaine (n=6–11 per group). Data are mean±SEM.

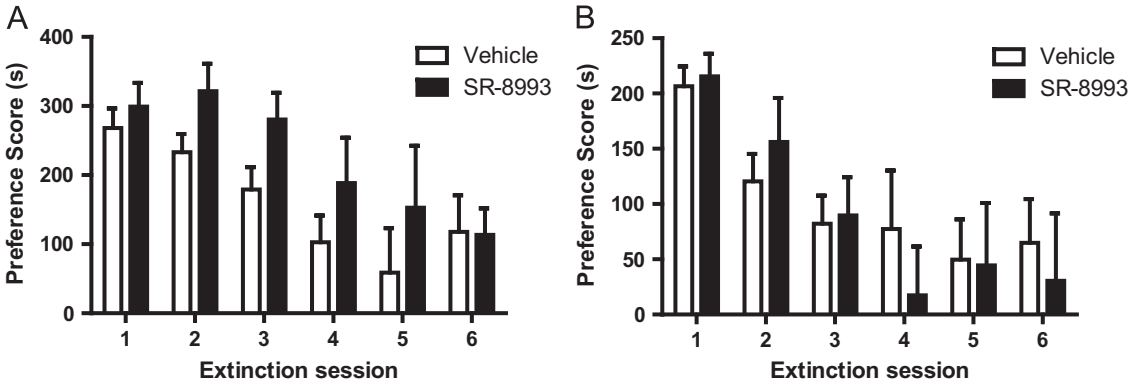

Fig. 3 – Effects of SR-8993 on extinction of cocaine CPP. Cocaine conditioned animals from both groups had similar preference scores in the initial, (drug-free) preference test (session 1). SR-8993 injections 30 min (A) or 2 h (B) prior to subsequent extinction tests (sessions 2–6) did not significantly alter CPP scores compared to vehicle-treated mice (n=6–7). Data are mean±SEM.

main effect was observed ($F_{2,16}$=1.7, p>0.05 at 30 min and $F_{2,20}$=0.1, p>0.05 at 2 h).

2.2. *Effects of SR-8993 on expression of cocaine CPP*

To examine the effects of NOP activation on the expression of cocaine CPP, mice were conditioned with 7.5 or 15 mg/kg of cocaine, and SR-8993 (3 mg/kg or 10 mg/kg) or vehicle was administered 30 min or 2 h prior to the CPP expression test. At both time points, SR-8993 failed to alter preference scores in mice conditioned with 15 mg/kg ($F_{2,28}$=0.5, p>0.05 for 30 min and $F_{2,21}$=0.5, p>0.05 for 2 h, Fig. 2A and B) or 7.5 mg/kg of cocaine ($F_{2,17}$=0.8 p>0.05 for 30 min and $F_{2,18}$=0.5, p>0.05 for 2 h, Fig. 2C and D). In a different group of animals, we found that SR-8993 (10 mg/kg) had no effect on locomotor activity compared to vehicle-treated animals (distance traveled in cm: *Veh*=1556±242; SR-8993=1716±261; t_9=0.4, p>0.05, n=5–6).

2.3. *Effects of SR-8993 on cocaine CPP extinction*

Next, we sought to determine whether SR-8993 (10 mg/kg) affects the rate of extinction when injected 30 min or 2 h before each extinction session. A two-way repeated measures ANOVA found a significant effect of time ($F_{5,65}$=8.0, p<0.0001 at 30 min, Fig. 3A and $F_{5,55}$=9.1, p<0.0001 at 2 h, Fig. 3B) but no interaction or group effect (p>0.05), indicating that SR-8993 has no overall effect on the rate of extinction compared to vehicle.

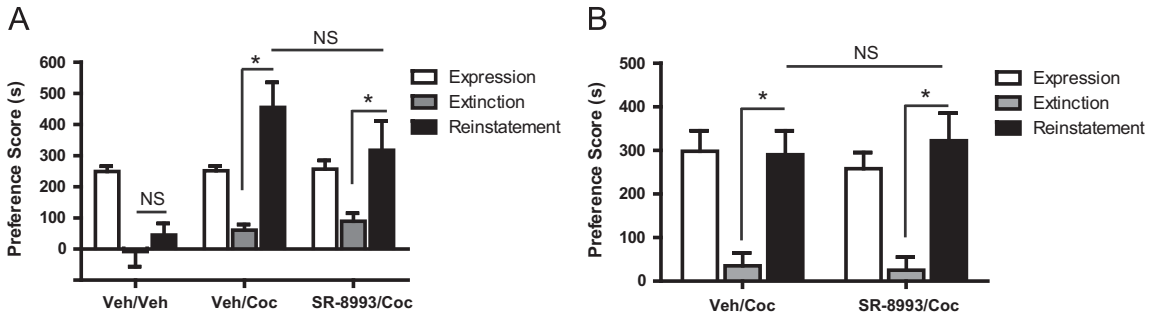

Fig. 4 – Effects of SR-8993 on cocaine-induced reinstatement of CPP. Conditioned mice showed similar preference during the expression test, and repeated exintction testing atteuated the place preference (A and B). A cocaine priming injection significantly reinstated the extinguished CPP, while mice treated with vehicle before testing did not show reinstatement (A). Injection of SR-8993 2 h (A) or 30 min (B) before reinstatement did not alter CPP scores compared to vehicle treated mice ($n=6$–8). $^{*}p<0.01$ via Bonferroni *post-hoc* test. Data are mean ± SEM.

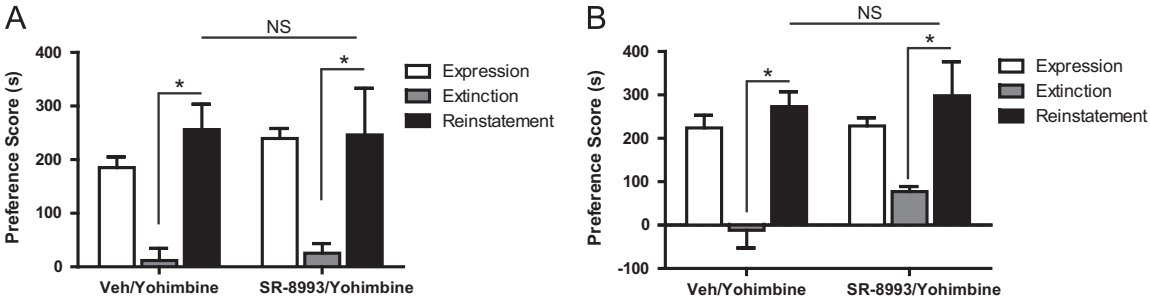

Fig. 5 – Effects of SR-8993 on yohimbine-induced reinstatement of CPP. Conditioned mice showed similar preference during the expression test, and repeated exintction testing atteuated the place preference (A and B). Yohimbine significantly reinstated the extinguished CPP, but SR-8993 injections 2 h (A) or 30 min (B) before the yohimbined-induced reinstatement test did not alter CPP scores compared to vehicle ($n=6$–7). $^{*}p<0.05$ via Bonferroni *post-hoc* test. Data are mean ± SEM.

2.4. *Effects of SR-8993 on cocaine- and yohimbine-induced reinstatement of CPP*

In subsequent experiments, we injected SR-8993 (10 mg/kg) 30 min or 2 h before cocaine- (10 mg/kg) or yohimbine-induced (2 mg/kg) reinstatement test. As a control, additional mice received a vehicle injection prior to reinstatement test. When mice were treated with SR-8993 or vehicle 2 h before cocaine-induced reinstatement test (Fig. 4A), a two-way ANOVA revealed a significant main effect of group ($F_{2,36}=6.9$, $p<0.01$), test ($F_{2,36}=19.9$, $p<0.0001$) and interaction ($F_{4,36}=5.2$, $p<0.01$). Bonferroni *post-hoc* test, however, found no difference in cocaine-induced reinstatement between vehicle- and SR-8993- treated mice ($p>0.05$). In mice injected with SR-8993 or vehicle 30 min before cocaine-induced reinstatement test (Fig. 4B), a two-way ANOVA revealed a significant effect of test ($F_{2,26}=34.7$, $p<0.0001$), but no significant group or interaction effect was observed ($p>0.05$). In mice injected with SR-8993 or vehicle 30 min or 2 h before yohimbine-induced reinstatement, a two-way ANOVA revealed a significant effect of test ($F_{2,24}=18.5$, $p<0.0001$ at 2 h, Fig. 5A and $F_{2,22}=21.0$, $p<0.0001$ at 30 min, Fig. 5B), but no significant group or interaction effect was observed ($p>0.05$).

3. Discussion

Recently, we demonstrated that administration of the selective NOP receptor agonist SR-8993 impaired consolidation of fear memories in animal models of post-traumatic stress disorder (Andero et al., 2013). Given that previous studies identified a role for nociceptin in the rewarding properties of cocaine (Kotlinska et al., 2002; Marquez et al., 2008; Rutten et al., 2010), and that similar neural mechanisms are known to be involved in stress- and reward-related behaviors (Koob and Kreek, 2007), we sought to determine whether SR-8993 would also affect behaviors related to cocaine reward and reinstatement. Using a conditioned place preference (CPP) procedure, we found that SR-8993 when injected 30 min or 2 h before testing did not significantly affect acquisition and expression of cocaine CPP when mice were conditioned 7.5 or 15 mg/kg of cocaine, nor did SR-8993 affect extinction, stress- or cocaine-induced reinstatement of CPP. These results indicate that selectively targeting the nociceptin receptor may not be sufficient for reducing cocaine reward-related behaviors.

Previous studies using nociceptin receptor agonists in cocaine-related behaviors have obtained mixed results. For example, Kotlinska et al. (2002) reported that intracranial delivery of nociceptin attenuated the expression of cocaine

CPP, but intraperitoneal administration of the NOP agonist, Ro65-6570, had no significant effect under the same conditions. Similarly, we also found that SR-8993 had no effect on expression of cocaine CPP. In a more recent study testing the effects of Ro65-6570 on the acquisition of cocaine CPP in rats, intraperitoneal delivery of Ro65-6570 increased the minimal effective dose of cocaine (but not dexamphetamine) required to induce a place preference (Rutten et al., 2010). However, Ro65-6570's affinity for NOP, mu- and delta-opioid receptors (Hashiba et al., 2001) prevents extrapolation that the effects of the drug are only due to nociceptin receptor agonism. Indeed, other mixed-action opioid/NOP compounds, such as buprenorphine, also attenuate the rewarding properties of cocaine (Kosten et al., 1991; Carroll and Lac, 1992; Sorge et al., 2005; Sorge and Stewart, 2006; Placenza et al., 2008). Here, we used SR-8993, which is known to have minimal affinity at mu and delta receptors, and at the concentrations used in the present study, SR-8993 is not likely to engage the other opioid receptors (Andero et al., 2013). Yet, it still did not affect acquisition of cocaine CPP. Thus, our current data indicates that selective activation of NOP with SR-8993 is not sufficient for altering behavioral responses to cocaine and that compounds with mixed NOP/opioid affinity are likely required to attenuate cocaine CPP.

3.1. *NOP in reinstatement of drug-seeking behaviors*

The effects of nociceptin receptor agonists on reinstatement and extinction of drug-seeking behaviors have also varied depending on the type of drug used. Shoblock et al. (2005) revealed that Ro64-6189 attenuated drug-primed reinstatement of morphine CPP but had no affect on extinction. In alcohol studies, Ro64-6198 reduced alcohol-induced reinstatement of CPP (Kuzmin et al., 2003), while the NOP receptor agonist MT-7716 prevented context- and stress-induced reinstatement of alcohol self-administration (Ciccocioppo et al., 2014; de Guglielmo et al., 2015). In another set of studies, intracranial delivery of nociceptin inhibited footshock- and cue-induced reinstatement of alcohol but not cocaine self-administration (Martin-Fardon et al., 2000; Ciccocioppo et al., 2004). Although SR-8993 did not affect extinction or reinstatement of cocaine CPP in our current study, our preliminary unpublished findings indicate that SR-8993 blocks stress- (yohimbine) and cue-induced reinstatement of alcohol self-administration (Aziz et al., 2014). Together, these data signify that selectively targeting the nociceptin system may attenuate relapse behaviors associated with morphine and alcohol but not cocaine.

3.2. *Mixed-action NOP/opioid ligands as a potential treatment for cocaine dependence*

Stimulation of the nociceptin receptor along with other opioid receptors may be necessary for therapeutic efficacy in treating cocaine addiction. For example, in animal studies, buprenorphine, a partial agonist at the mu-opioid and NOP receptors and antagonist at kappa- and delta opioid receptors (Cowan et al., 1977; Sadee et al., 1982), has been shown to attenuate cocaine self-administration, CPP and sensitization (Kosten et al., 1991; Carroll and Lac, 1992; Sorge et al., 2005; Sorge and Stewart, 2006; Placenza et al., 2008). In clinical studies, high doses of buprenorphine, such as those that would be required to activate NOP, showed efficacy in treating cocaine use in addicted individuals (Schottenfeld et al., 1993). Buprenorphine in combination with naltrexone (to block buprenorphine's activity at the mu opioid receptor) also reduced cocaine self-administration under short and extended access conditions and reinstatement of cocaine CPP in animals (Mello et al., 1993; Wee et al., 2012; Cordery et al., 2014), suggesting that buprenorphine's affinity for receptors other than mu (potentially kappa, delta and/or NOP) contribute to its anti-addiction effects. Therefore, treatment of cocaine addiction may be more effectively achieved by mixed agonist–antagonist opioid receptor modulators.

4. Experimental procedures

4.1. *Animals*

Male c57bl/6 mice (8–10 weeks old, Charles River Laboratories) were housed 2–4 animals per cage under a regular 12 h/12 h light/dark cycle and had *ad libitum* access to food and water. Mice were housed in a humidity and temperature-controlled, AAALAC-accredited, animal facility at the University of Miami Miller School of Medicine. All experiments were approved by the Institutional Animal Care and Use Committee (IACUC) and conducted according to specifications of the NIH as outlined in the Guide for the Care and Use of Laboratory Animals.

4.2. *Drug treatments*

Cocaine HCl (NIDA, Research Triangle Park, NC) was dissolved in 0.9% sterile saline. Animals received intraperitoneal (i.p.) injections of saline or cocaine (7.5, 10 or 15 mg/kg) during behavioral testing. The nocicpetin receptor agonist SR-8993 and naloxone (Tocris) was dissolved in saline; 3–10 mg/kg of SR-8993 and 5 mg/kg of naloxone was given in a volume of 0.08–0.1 ml in behavioral tests described below. Vehicle (saline) was delivered at the same volume as the drug solution. SR-8993 is highly selective when tested in a panel of GPCRs, ion channels and transporters and showed >50-fold selectivity over all receptors tested (Andero et al., 2013). The doses for all drugs were based on their salt form.

4.3. *Conditioned place preference*

In conditioned place preference experiments, we utilized previously published methods (Sartor and Aston-Jones, 2012; Sartor et al., 2015). Briefly, the CPP apparatus consisted of 2 distinct environments that were separated by a removable divider. In a pre-test, mice freely explored both environments for 15 min via an opening in the divider. EthoVision tracking software was used to measure the time spent on each side of the CPP chamber. Groups were then organized such that mean baseline pre-test scores were not different between treatments. On the next 3 days of conditioning, mice were injected with cocaine (7.5 or 15 mg/kg, i.p.) and confined to one side of the chamber by a solid divider for 30 min, or

injected with saline and restricted to the other side of the chamber for 30 min. As a control, additional mice received a saline injection on both sides of the chamber. Injections during conditioning were administered in a balanced fashion in morning and afternoon sessions (at least 4 h apart). Conditioned animals were then given a 15-minute post-test. To test the role of SR-8993 in the acquisition of cocaine CPP, vehicle or SR-8993 (3 or 10 mg/kg, i.p.) was injected 30 min or 2 h before each cocaine conditioning session. To test CPP expression, SR-8993 (3 or 10 mg/kg, i.p.) or vehicle was injected 30 min or 2 h before the CPP test. Injecting 30 min or 2 h before testing was based on SR-8993's half-life and previous behavioral data showing that this regimen reduced fear conditioning and ethanol-seeking in rodents (Andero et al., 2013; Aziz et al., 2014). To demonstrate that we could attenuate cocaine CPP, naloxone (NLX, 5 mg/kg, i.p.) was given 10 min before cocaine conditioning sessions as it has previously been shown to reduce cocaine place preference (Kim et al., 1997).

For extinction experiments, conditioned animals were first given a drug-free preference test (session 1) in order to confirm CPP and to balance treatment groups based on initial CPP scores. For the next 5 sessions (one session per day, sessions 2–6) SR-8993 (10 mg/kg) or vehicle was administered 30 min or 2 h before each passive extinction test in which each animal had free access to both sides of the chamber. In reinstatement experiments, additional animals were passively extinguished by giving a drug-free CPP test each day until preference scores were reduced by at least 50% for two consecutive days. In cocaine-primed reinstatement tests, SR-8993 (10 mg/kg) or vehicle was administered 30 min or 2 h before the cocaine-primed (10 mg/kg) reinstatement test, and cocaine was injected immediately before testing. As a control, additional mice received vehicle injections (vehicle/vehicle group) prior to the reinstatement test. For stress-induced reinstatement, SR-8993 (10 mg/kg) or vehicle was administered 30 min or 2 h before yohimbine-induced (2 mg/kg, i.p.) reinstatement test. Yohimbine was injected 30 min before testing.

4.4. *Locomotor test*

Distance traveled was measured in a 27×27 cm^2 open field chamber using EthoVision tracking software. Baseline locomotor behavior was measured in a 15 min habituated test. Animals were grouped such that baseline locomotor activity did not differ between groups. Next, animals were injected with SR-8993 (10 mg/kg) or vehicle and were placed back in their home cage. Two hours later (when SR-8993 concentration peaks in the brain), animals received another 15-minute locomotor test.

4.5. *Data analysis*

Graphpad Prism software was used for graph preparation and statistical analysis. Preference scores were analyzed by calculating the time spent in the cocaine-paired side on post-test minus the time spent in the cocaine-paired side during pre-test. In acquisition and expression experiments, mean values from CPP preference scores were compared between groups using a one-way analysis of variance (ANOVA). Extinction data were analyzed with a two-factor repeated measures ANOVA with group as the between-subjects factor and session number as the repeated factor. A two-factor repeated measures ANOVA with group as the between-subjects factor and test condition (expression, extinction and reinstatement) as the repeated factor was used to compare groups during reinstatement. When a significant *F*-value was obtained, comparisons were carried out using Newman–Keuls or Bonferroni *post-hoc* analysis. Data are mean $\pm$SEM, and the level of significance was set to 0.05.

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