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Lorcaserin suppresses oxycodone self-administration and relapse vulnerability in rats

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Abstract

Opioid use disorder (OUD) is a major public health problem. High relapse rates and poor treatment retention continue to pose major challenges in OUD treatment. Of the abused opioids, oxycodone is well described to maintain self-administration and evoke the durable conditioned responses ("cue reactivity") that result from pairing of opioid-related stimuli (e.g., paraphernalia) with repeated abuse. Serotonin (5-HT) neurotransmission, particularly through the 5-HT_{2C} receptor (5-HT_{2C}R), regulates psychostimulant reward and cue reactivity, and in the present experiments, we investigated the hypothesis that the selective 5-HT_{2C}R agonist lorcaserin, which is FDA-approved for the treatment of obesity, will suppress oxycodone self-administration and oxycodone-associated cue reactivity in rats. We found that lorcaserin inhibited oxycodone intake, an effect blocked by the selective 5-HT_{2C}R antagonist SB242084. Lorcaserin also decreased responding for the discrete cue complex ("cue reactivity") previously associated with delivery of oxycodone (i.e., stimulus lights, infusion pump sounds) in both abstinence and extinction-reinstatement models. The selected dose range of lorcaserin (0.25–1 mg/kg) does not overtly alter spontaneous behaviors nor operant responding on inactive levers in the present study. Taken together, the ability of lorcaserin to reduce the oxycodone self-administration and decrease cue

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The remaining authors declare no competing financial interests.

Author Contributions

H.N. carried out behavioral pharmacological evaluations and drafted the manuscript. E.D.H. conducted statistical analyses and edited the manuscript. R.G.F. and S.J.S. carried out behavioral pharmacological evaluations. N.C.A. and K.A.C. supervised the experimental design, conduct and interpretation of studies. S.D.C., M.H., F.G.M., N.C.A. and K.A.C. conceptualized the project, designed, analyzed and interpreted experiments, and wrote/edited the manuscript.

reactivity associated with relapse highlights the therapeutic potential for lorcaserin in the treatment of OUD.

INTRODUCTION

The epidemic of opioid use disorder (**OUD**) is one of the top public health problems in the United States.[1–2] The misuse of prescription (e.g., oxycodone) and illicit opioids (e.g., heroin) can escalate into OUD with significant morbidity and mortality.[3–4] Treatment goals for OUD include mitigation of opioid-induced withdrawal and attainment of long-term abstinence.[5] Pharmacotherapeutics development for OUD has focused largely on μ-opioid ligands given that abused opioid analgesics share efficacy as μ-opioid receptor agonists (for review).[6] Medications that act as long-acting μ-opioid agonists (e.g., methadone), partial agonists (e.g., buprenorphine) as well as antagonists (e.g., naltrexone) have been employed to promote recovery within a suitably supportive therapeutic environment.[5,7] However, high relapse rates and poor treatment retention continue to pose major challenges in the treatment of OUD.

Environmental context(s) and stimuli (e.g., paraphernalia) which become associated with substance use lead to enduring conditioned responses (“cue reactivity”) that can precipitate relapse.[8–9] Drug cue reactivity is measurable as conditioned physiological (e.g., elevated heart rate) and subjective responses (e.g., craving) as well as attentional orienting behaviors (e.g., drug-seeking) and limbic-corticostriatal circuit activation in humans,[8,10–12] including opioid users.[13–22] Furthermore, measures of cue reactivity predict relapse in abstinent heroin users following detoxification,[23] while the cue-induced cortisol response correlates with subsequent opioid use in opiate-abstinent methadone and buprenorphine-treated patients.[15] Thus, novel treatment strategies effective at reducing cue reactivity as well as opioid intake may be particularly effective to promote recovery from OUD.

Serotonin (5-HT) neurotransmission confers modulatory control over the limbic-corticostriatal circuitry engaged in drug reward and cue reactivity, particularly through the 5-HT_{2C} receptor (5-HT_{2C}R) (for reviews).[24–26] Activation of the 5-HT_{2C}R following systemic administration of the FDA-approved anti-obesity medication lorcaserin (Belviq®) or investigational, selective 5-HT_{2C}R agonists (e.g., Ro 60–0175, WAY163909) has been shown to suppress self-administration of cocaine[27–34] and nicotine in preclinical models.[35–39] Similarly, selective 5-HT_{2C}R agonists have been shown to suppress cue reactivity assessed in both cocaine[28,30–32,40–41] and nicotine self-administration assays.[36–37,42] However, much less is known about the involvement of the 5-HT_{2C}R in the modulation of the reward-related behavioral effects of opioids.

One of the most commonly abused opioids in the United States is oxycodone, a semisynthetic opioid which accounts for a significant number of emergency department visits in the United States.[43] Oxycodone binds to the μ-opioid receptor preferentially, but is metabolized *in vivo* to oxymorphone which is also a potent and highly efficacious μ-opioid agonist.[44–46] Oxycodone is self-administered by rats and monkeys, and its reinforcing effects are blocked by μ-opioid antagonists (e.g., naltrexone).[47–51] In the present study, we trained rats to self-administer oxycodone (0.1 mg/kg/infusion) and investigated the

hypothesis that lorcaserin would suppress intake of oxycodone and cue reactivity in rats. Lorcaserin is a high-affinity, full agonist at the human 5-HT_{2C}R with selectivity over the 5-HT_{2A}R (18-fold) and 5-HT_{2B}R (104-fold), sites at which lorcaserin is a partial and full agonist, respectively.[52] The predicted blood concentration required to activate peripheral 5-HT_{2A}R and 5-HT_{2B}R would be ~250-fold and ~1,400-fold, respectively, above concentrations necessary to stimulate the full-length 5-HT_{2C}R[52] which is found only in the central nervous system.[53–55]

The design of most analyses of cue reactivity in rodents includes acquisition of drug self-administration followed by extinction and subsequent reinstatement sessions in the presence of the drug-associated environment.[28,56–57] Cue reactivity is also assessed in the absence of extinction training.[24,32,58–59] In these models, lever presses during cue reactivity test sessions are recorded and may or may not result in the delivery of drug-associated cues (for reviews).[60–61] Given that the neuroadaptations determined following extinction training *versus* during forced abstinence are distinct,[62–65] we assessed the effects of lorcaserin on cue reactivity in both the abstinence and extinction-reinstatement models. In both models, lever presses during the cue reactivity test sessions were reinforced with the discrete cue complex (i.e., stimulus lights, infusion pump sounds) which had previously been paired with oxycodone delivery. Our findings indicate that lorcaserin suppresses oxycodone intake as well as cue reactivity, which suggests that lorcaserin may be therapeutically useful for promoting abstinence and preventing relapse in OUD.

RESULTS AND DISCUSSION

Lorcaserin suppresses oxycodone self-administration

Rats acquired oxycodone self-administration (0.1 mg/kg/0.1 ml infusion) to stability, displaying <10% variation in the number of infusions received over the session (Fig. 1A). Across the last three sessions of stable oxycodone self-administration, there was no main effect of session on the number of infusions obtained [$F_{(2,27)} = 0.91$; ns], active [$F_{(2,27)} = 0.84$; ns] or inactive lever presses [$F_{(2,27)} = 0.76$; ns]. The average daily oxycodone intake over the last three sessions of training was 2.4 ± 0.2 mg/kg (mean ± SEM).

Lorcaserin (0.25, 0.5 or 1 mg/kg; s.c.) or vehicle was administered 15 min prior to self-administration sessions while SB 242084 (0.5 mg/kg; i.p., 30 min) pretreatment was administered prior to vehicle or lorcaserin (1 mg/kg, i.p.; 15 min). A one-way ANOVA revealed a main effect of pretreatment on oxycodone infusions obtained [$F_{(5,54)} = 4.10$; $p < 0.05$] and active [$F_{(5,54)} = 5.64$; $p < 0.05$], but not inactive lever, presses [$F_{(5,54)} = 1.28$; ns]. *A priori* comparisons revealed that lorcaserin (1 mg/kg) significantly reduced oxycodone infusions obtained ($p < 0.05$; Fig. 1B, **left panel**) and active lever presses (data not shown) relative to vehicle; inactive lever presses were unaffected (data not shown). The selective 5-HT_{2C}R antagonist SB 242084 (0.5 mg/kg; i.p.) blocked the effects of lorcaserin (1 mg/kg) on oxycodone infusions obtained ($p < 0.05$, Fig. 1B, **right panel**) and active lever presses ($p < 0.05$; data not shown); inactive lever presses were not altered (ns; data not shown).

Figure 1C illustrates the effects of the three test doses of lorcaserin (0.25–1 mg/kg) on the cumulative infusions across session time. A mixed model ANOVA revealed a main effect of

lorcaserin dose [$F_{(3,36)} = 6.77$; $p < 0.05$] and time [F(5,36 = 418.91; $p < 0.05$], but no lorcaserin dose X time interaction [$F_{(15,180)} = 1.58$; ns], on oxycodone infusions obtained. *A priori* comparisons revealed that lorcaserin (1 mg/kg) significantly reduced oxycodone infusions obtained relative to vehicle at all time points (Fig. 1C). This time course for the efficacy of lorcaserin to suppress oxycodone intake over the 180-min session is consistent with the reported pharmacokinetic parameters for lorcaserin (1–2 mg/kg) in male Sprague-Dawley rats [half-life ($t_{1/2}$) ~2–3.5 h].[35,68]

Lorcaserin suppresses oxycodone cue reactivity in an abstinence model

We tested the hypothesis that lorcaserin will suppress cue reactivity 24 hours after the last oxycodone self-administration session. Rats readily acquired oxycodone self-administration to stability (Fig. 2A). Across the last three sessions of stable oxycodone self-administration, there was no main effect of session on infusions [$F_{(2,87)} = 0.64$, ns], active [$F_{(2,87)} = 0.59$, ns] or inactive lever presses [$F_{(2,87)} = 0.87$, ns]. The average daily oxycodone intake over the last three sessions of training was 1.9 ± 0.1 mg/kg (mean ± SEM).

Lorcaserin (0.25–1 mg/kg) or vehicle was administered 15 min prior to the test session. A one-way ANOVA revealed a main effect of lorcaserin pretreatment on previously active [$F_{(3,26)} = 8.65$; $p < 0.05$], but not inactive lever presses [$F_{(3,26)} = 2.29$; ns]. *A priori* comparisons revealed that pretreatment with lorcaserin (1 mg/kg) significantly decreased previously active lever presses relative to vehicle ($p < 0.05$; Fig 2B). The latency to the first lever press following pretreatment with lorcaserin was unaltered [$F_{(3,26)} = 0.93$; ns; data not shown]. These data suggest that lorcaserin suppresses oxycodone cue reactivity in a model that does not include extinction training.

Lorcaserin suppresses cue reactivity in the extinction-reinstatement model

We tested the hypothesis that lorcaserin will suppress cue reactivity after extinction from oxycodone self-administration. Rats were trained to self-administer oxycodone to stability (Fig. 3A). Across the last three sessions of stable oxycodone self-administration, there was no main effect of session on infusions [$F_{(2,27)} = 0.13$, ns], active [$F_{(2,27)} = 0.18$, ns] or inactive lever presses [$F_{(2,27)} = 0.64$, ns]. The average daily oxycodone intake over the last three sessions of training was 1.9 ± 0.2 mg/kg (mean ± SEM).

Stable acquisition of oxycodone self-administration in this cohort was followed by daily, 60-min extinction sessions; during these sessions, active and inactive lever presses were recorded but had no scheduled consequences. Presses on the previously active lever decreased across extinction sessions with all rats achieving extinction criteria (<15 total responses/hour for three consecutive sessions) (data not shown). A main effect of extinction session on previously active [$F_{(11,84)} = 6.88$; $p < 0.05$], but not inactive lever, presses [$F_{(11,84)} = 1.07$; ns] was observed. The “extinction baseline” was calculated as the mean total lever presses of all rats on the active (9.2 ± 2.9) or inactive lever (5.8 ± 1.1) during the last 60-min extinction session (Fig. 3B).

Lorcaserin (0.25–1 mg/kg) or vehicle was administered 15 min prior to the test session. A one-way ANOVA revealed a main effect of lorcaserin pretreatment on previously active [$F_{(3,36)} = 8.39$; $p < 0.05$], but not inactive, lever presses [$F_{(3,36)} = 0.75$; ns]. *A priori*

comparisons revealed that pretreatment with lorcaserin (0.5 and 1 mg/kg) significantly reduced previously active lever presses relative to vehicle ($p < 0.05$; Fig. 3B). The latency to the first lever press following pretreatment with lorcaserin was unaltered [$F_{(3,36)} = 2.44$; ns] (data not shown). In contrast to the abstinence model, greater sensitivity of cue reactivity to lorcaserin-evoked suppression is evident following extinction training.

We found that the selective 5-HT_{2C}R agonist lorcaserin inhibited oxycodone intake, an effect blocked by the selective 5-HT_{2C}R antagonist SB242084. Lorcaserin also decreased responding for the discrete cue complex previously associated with delivery of oxycodone in both the abstinence and extinction-reinstatement models in rodents. The selected dose range of lorcaserin (0.25–1 mg/kg) employed here did not overtly alter spontaneous behaviors[37–38] nor operant responding on inactive levers or the latency to the first press in the present study. Taken together, these data suggest that lorcaserin reduced reward-related effects of oxycodone which cannot be explained by non-specific, rate-decreasing effects of lorcaserin.

Serotonin-enhancing drugs have been shown to modulate opioid-induced behavioral effects in animals. Administration of the selective serotonin reuptake inhibitor fluoxetine during withdrawal from chronic opioid exposure, a period during which brain 5-HT levels are diminished,[69] ameliorated physical signs of naloxone-precipitated withdrawal[70] and subjective measures (i.e., preference for an opioid-associated environment and anxiety-like measures) in opioid-withdrawn rodents.[71] Systemic administration of 5-HT releasers (i.e., dexfenfluramine, fenfluramine) suppressed heroin self-administration in rats[72–73] and attenuated the discriminative stimulus effects of morphine in monkeys,[74] behavioral effects that might involve the 5-HT_1R and 5-HT_2R subtypes.[72–73] Interestingly, recent studies found that lorcaserin reduced opioid-induced behavioral sensitization and ameliorated physical signs of naloxone-precipitated withdrawal following chronic opioid exposure in mice.[75–76] These studies suggest that 5-HT neurotransmission can critically influence aspects of opioid-evoked behaviors potentially via engagement of the brain 5-HT_{2C}R system in keeping with the present study. Future experiments are required to extend these observations to a broader dose range for oxycodone self-administration and lorcaserin pretreatment as well as analysis of the effects of lorcaserin upon chronic administration.

Opioids bind with high affinity to μ-opioid receptors localized to ventral tegmental area (VTA) dopamine neurons which innervate the nucleus accumbens (NAc) to comprise a key component of the neural circuitry underlying both drug and natural reward-motivated behaviors (for reviews).[77–80] A μ-opioid receptor agonist (e.g., morphine) microinjected into the VTA supports self-administration,[81–83] while intra-VTA infusion of a μ-opioid receptor antagonist resulted in a compensatory enhancement of heroin self-administration.[84] Opioid agonists selective for the μ-opioid receptor hyperpolarize VTA γ-aminobutyric acid (GABA) interneurons in the VTA resulting in a loss of tonic GABA inhibition over VTA neurons,[85] increased firing rates of VTA dopamine neurons and enhanced dopamine release in the NAc.[85–86] This indirect mechanism of opioid receptor regulation of VTA output is widely considered to mediate the reward-related behavioral effects of opioid analgesics[77–80] (but see).[87]

The μ-opioid receptor and the 5-HT_{2C}R could functionally interface at the level of the VTA to control oxycodone self-administration. The 5-HT_{2C}R is expressed on VTA GABA interneurons and projection neurons.[88–91] Stimulation of the 5-HT_{2C}R triggers a signaling cascade that results in membrane depolarization and neuronal firing,[92–94] and has been shown to increase the firing rate of GABA interneurons,[88, 95] enhance basal GABA release in the VTA,[96] and decrease firing rates of VTA dopamine neurons.[88, 95] The 5-HT_{2C}R is also expressed on a subset of dopamine VTA neurons[89–90] and functions as a key regulator of their physiology in mice.[97] These findings suggest the possibility that lorcaserin may directly regulate oxycodone self-administration via actions at the 5-HT_{2C}R localized to the VTA,[98] although further experimentation is required to explore the functional mechanisms through which the VTA μ-opioid receptor and the 5-HT_{2C}R interact. This site of action for the 5-HT_{2C}R may also control oxycodone cue reactivity as suggested for cocaine,[99] although corticostriatal involvement should be considered given that the functional status of the 5-HT_{2C}R system in the medial prefrontal cortex is a key contributor to cocaine cue reactivity.[24,32,41]

The efficacy of lorcaserin to reduce oxycodone self-administration and decrease cue reactivity associated with relapse highlights the therapeutic potential for lorcaserin in the treatment of OUD. Furthermore, the observation that selective 5-HT_{2C}R agonists suppress self-administration and cue reactivity associated with abused drugs across psychostimulant and opioid classes is intriguing, and future studies are required to appreciate the overlapping mechanisms and sites of action for the 5-HT_{2C}R to control reward-related behaviors.

METHODS

Animals

Male Sprague-Dawley rats (n=72; Harlan, Inc., Houston, TX) weighing 250–325 g at the start of experiments were used. Rats were acclimated for seven days in a colony room maintained at a constant temperature (21–23°C) and humidity (45–50%) on a 12-hour light-dark cycle (lights on 0600–1800 h). Rats were housed two/cage and handled daily throughout the study. Food and water were available *ad libitum* throughout all phases of the studies. All experiments were carried out in accordance with the National Institutes of Health *Guide for the Care and Use of Laboratory Animals* (2011) and with approval from the University of Texas Medical Branch Institutional Animal Care and Use Committee.

Drugs

Oxycodone hydrochloride [Sigma, Research Triangle Park, NC] and lorcaserin hydrochloride (Hangzhou Trylead Chemical Technology Co., Ltd., Hangzhou, China) were dissolved in 0.9% NaCl. SB 242084 (6-chloro-5-methyl-1-[[2-(2-methylpyrid-3-yloxy) pyrid-5-yl]carbamoyl]indolinedihydrochloride; Sigma Chemical Co., St. Louis, MO, USA) was dissolved in 0.9% NaCl containing 10 mM citric acid (Sigma Chemical Co.) and 8% 2-hydroxypropyl-β-cyclodextrin (Trappsol®, Cyclodextrin Technologies Development Inc., High Springs, FL, USA) with the final pH of the solution adjusted to 5.6.

Surgical implantation of intravenous catheters

Implantations of intravenous catheters with back mounts were performed under anesthesia with a cocktail containing 8.6 mg/kg of xylazine, 1.5 mg/kg of acepromazine, and 43 mg/kg of ketamine in bacteriostatic saline and allowed to recover for 5–7 days.[24,28,41,66] Catheter patency was maintained by daily flushes with a solution of 0.1 mL bacteriostatic saline containing heparin sodium (10 U/mL; American Pharmaceutical Partners, East Schaumburg, IL), streptokinase (0.67 mg/mL; Sigma Chemical), and ticarcillin disodium (66.67 mg/mL; Research Products International, Mt. Prospect, IL) immediately following daily oxycodone self-administration sessions. Proper catheter function was verified periodically throughout experiments by intravenous administration of 10 mg/kg of methohexital sodium (Monarch Pharmaceuticals Inc., Bristol, TN), a dose sufficient to briefly anesthetize the animal only when administered intravenously. All rats were allowed 5–7 days of recovery after surgery before initiation of self-administration training.

Self-administration training

Standard operant conditioning chambers (Med-Associates, Inc., St. Albans, VT, USA) housed in ventilated, sound-attenuating cubicles with fans (Med-Associates, Inc.) were utilized for oxycodone self-administration studies. Each chamber was equipped with a pellet receptacle flanked by two retractable response levers, a stimulus light above each response lever, and a house light opposite the levers. Oxycodone infusions were delivered via syringes attached to infusion pumps (Med-Associates, Inc.) located outside the cubicle. The infusion pumps were connected to liquid swivels (Instech, Plymouth Meeting, PA) that were fastened to the catheters via polyethylene 20 tubing encased inside a metal spring leash (Plastics One, Roanoke, VA).

Freely fed rats were trained to lever press for oxycodone infusions (0.1 mg/kg/0.1 mL infusion) using established methods.[24,28,41,66] The training dose for oxycodone (0.1 mg/kg/0.1 mL infusion) was chosen according to previous studies;[49–50] preliminary data demonstrated this dose maintained stable self-administration in rats. Oxycodone self-administration training consisted of daily 180-min sessions during which rats were trained to press the active lever to obtain an infusion on a fixed ratio (FR) 1–3 schedule of reinforcement before progressing to an FR5 schedule. Schedule completions on the active lever resulted in delivery of an oxycodone infusion over a 6-sec period paired simultaneously with illumination of the house and stimulus lights and activation of the infusion pump (discrete cue complex); inactive lever presses produced no scheduled consequences. Following reinforcer delivery, the stimulus light and infusion pump were inactivated; the house light remained on for an additional 20 sec to indicate a timeout period during which lever presses had no scheduled consequences. The criterion for stable self-administration (<10% variation in the number of infusions obtained for three consecutive sessions) was achieved prior to initiation of test sessions. Cue reactivity test sessions proceeded with the rats tethered to catheters and placed in chambers as in self-administration sessions; previously active lever presses resulted in delivery of cues without fluid delivery. Due to diminished catheter patency in some rats (n=22), n=50 rats were included in the analyses.

RESEARCH DESIGN

Lorcaserin effects on oxycodone self-administration

In rats (n=10) trained to self-administer oxycodone (0.1 mg/kg/inf) to stability, the efficacy and specificity of lorcaserin to alter oxycodone intake were assessed. Lorcaserin (0.25, 0.5 or 1 mg/kg) or vehicle was injected subcutaneously (s.c.) 15 min prior to the oxycodone self-administration session in a within subjects design. Doses and pretreatment times for lorcaserin were chosen based on previous studies,[27,35–38] and tests were administered in a pseudorandomized order with a minimum of two intervening sessions of oxycodone self-administration to assure stability of baseline responding. To investigate the dependency of effects on the 5-HT_{2C}R, the selective 5-HT_{2C}R antagonist SB 242084 (0.5 mg/kg; s.c.)[28] was administered at 30 min prior, followed by lorcaserin (1 mg/kg, i.p.) or vehicle intraperitoneally (i.p.) 15 min prior to the self-administration test session.

Lorcaserin effects on oxycodone cue reactivity

In rats trained to self-administer oxycodone to stability, we assessed the effects of lorcaserin on cue reactivity in both the abstinence and extinction-reinstatement models. In the abstinence cohort (n=30), lorcaserin (0.25, 0.5, or 1 mg/kg) or vehicle was administered s.c. 15 min prior to the 60-min test session in a between subjects design. Cue reactivity tests were conducted at 24 hours of abstinence from oxycodone self-administration. Rats were placed in operant chambers and lever presses on the previously active lever were reinforced by the discrete cue complex (house and stimulus light illuminated, infusion pump activated) on an FR1 schedule; presses on the inactive lever were recorded, but produced no scheduled consequences.

Rats in the second cohort (n=10) were subjected to daily 60-min extinction sessions after achieving stable self-administration. Extinction sessions were conducted during which active and inactive lever presses were recorded, but had no scheduled consequences. Once rats achieved the extinction criterion of response rates <15 total responses/hour for three consecutive sessions, lorcaserin (0.25, 0.5, or 1 mg/kg) or vehicle was injected s.c. 15 min prior to the 60-min session in a within subjects design. A single, non-response contingent presentation of the discrete cue complex initiated the cue reactivity test. During the session, responses on the previously active lever were reinforced by the discrete cue complex on an FR1 schedule; presses on the inactive lever were recorded but produced no scheduled consequences. Rats in this cohort completed all test sessions; the order of injections was pseudorandomized with a minimum of three intervening extinction sessions occurring between each drug challenge to assure stability of extinction criterion (<15 total responses/hr).

Statistical analyses

All pharmacological manipulations were conducted by an experimenter blinded to the test conditions. A one-way analysis of variance (ANOVA) for a within subjects design was employed to assess (a) oxycodone infusions, (b) active or previously active, and (c) inactive lever responses during self-administration for all cohorts. A mixed model ANOVA for the factors of lorcaserin dose and session time bin (30–180 mins) across the oxycodone self-

administration test session was conducted. In the abstinence cohort, a one-way ANOVA for a between subjects design was employed to assess (a) previously active, (b) inactive lever presses, and (c) latency to respond on the previously active lever during cue reactivity test sessions. A one-way ANOVA for a within subjects design was used to assess (a) previously active, and (b) inactive lever presses during extinction sessions and cue reactivity tests after extinction. In the abstinence cohort, the between subjects design indicated a lorcaserin-induced suppression of oxycodone cue reactivity; hence, the within subjects design was employed in the extinction-reinstatement cohort to increase power and reduce the number of rats required. *A priori* comparisons were defined prior to the start of experimentation and conducted by Dunnett's procedure or Student–Newman–Keuls test.[67] Analyses were conducted with SAS for Windows (Version 9.4, SAS Institute, Inc., Cary, NC) with an experiment-wise error rate set at α=0.05.

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ABBREVIATIONS

5-HT	serotonin (5-hydroxytryptamine)
5-HT$_1$R	5-HT1 receptor
5-HT$_{2C}$R	5-HT$_{2C}$ receptor
OUD	Opioid use disorder
NAc	nucleus accumbens
VTA	ventral tegmental area

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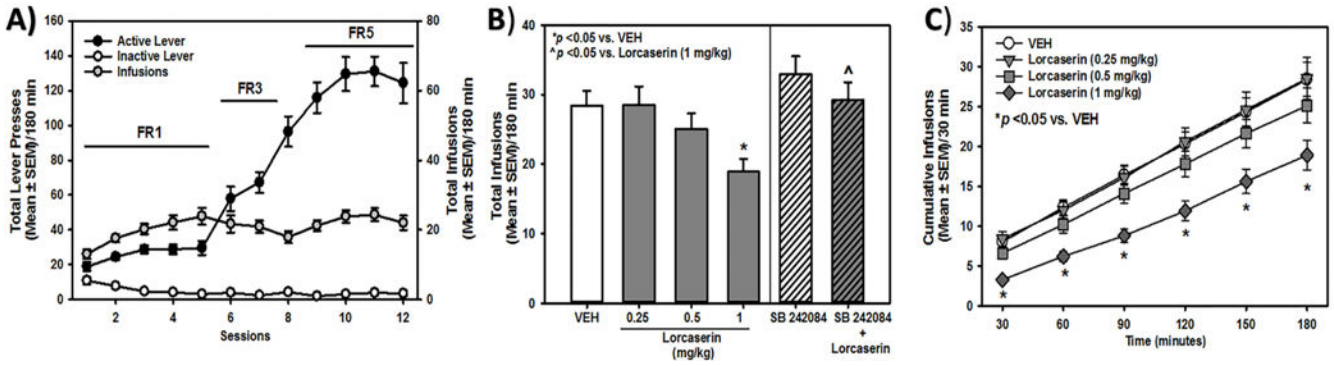

Figure 1. Lorcaserin suppresses oxycodone self-administration

[A] Total presses (mean ± SEM) on the active (black circles) or inactive lever (white circles; left X-axis), and total number of oxycodone infusions obtained (gray circles; right X-axis) are presented for the acquisition of oxycodone self-administration. **[B]** The effects and specificity of lorcaserin (0.25, 0.5, 1 mg/kg) to alter total oxycodone infusions (mean ± SEM) are presented. Lorcaserin (1.0 mg/kg) suppressed oxycodone intake relative to vehicle (*$p < 0.05$ vs. VEH; **left panel**) while pretreatment with SB 242084 (0.5 mg/kg; **right panel**) reversed the effects of lorcaserin (1.0 mg/kg) (^ $p < 0.05$ vs. 1 mg/kg of lorcaserin). **[C]** The effects of lorcaserin (0.25, 0.5, 1 mg/kg) or vehicle (VEH) on cumulative oxycodone infusions (mean ± SEM) are presented. Lorcaserin (1.0 mg/kg) suppressed oxycodone intake across all time bins (* $p < 0.05$ vs. VEH).

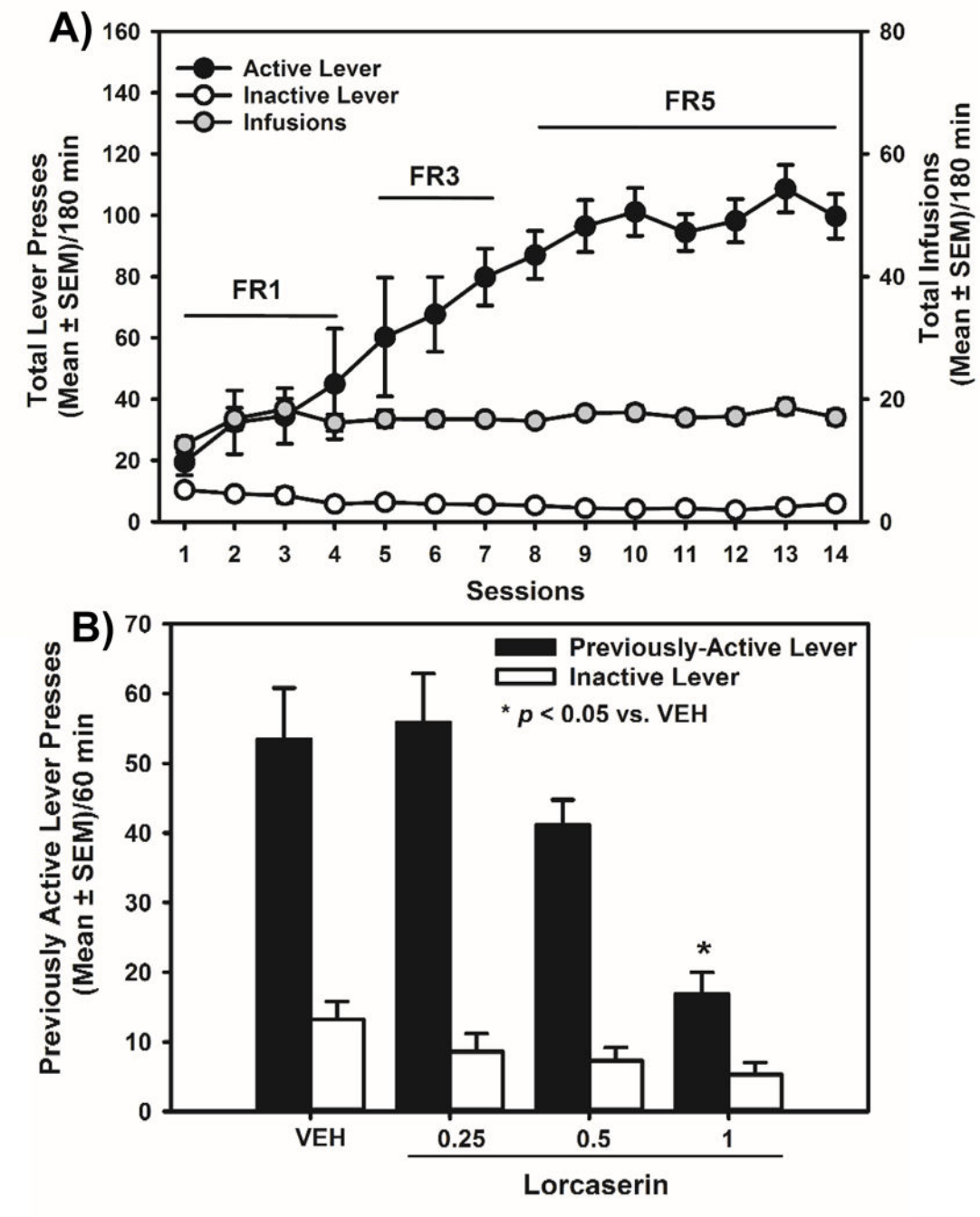

Figure 2. Lorcaserin suppresses oxycodone cue reactivity in the abstinence model

[A] Total presses (mean ± SEM) on the active (black circles) or inactive lever (white circles; left X-axis), and total number of oxycodone infusions obtained (gray circles; right X-axis) are presented for the acquisition of oxycodone self-administration. **[B]** The effects of lorcaserin (0.25, 0.5, 1 mg/kg) on previously active and inactive lever presses (mean ± SEM) at 24 hrs of abstinence from the last self-administration session are presented. Lorcaserin (1.0 mg/kg) suppressed previously active, but not inactive, lever presses, relative to vehicle (*$p < 0.05$ vs. VEH).

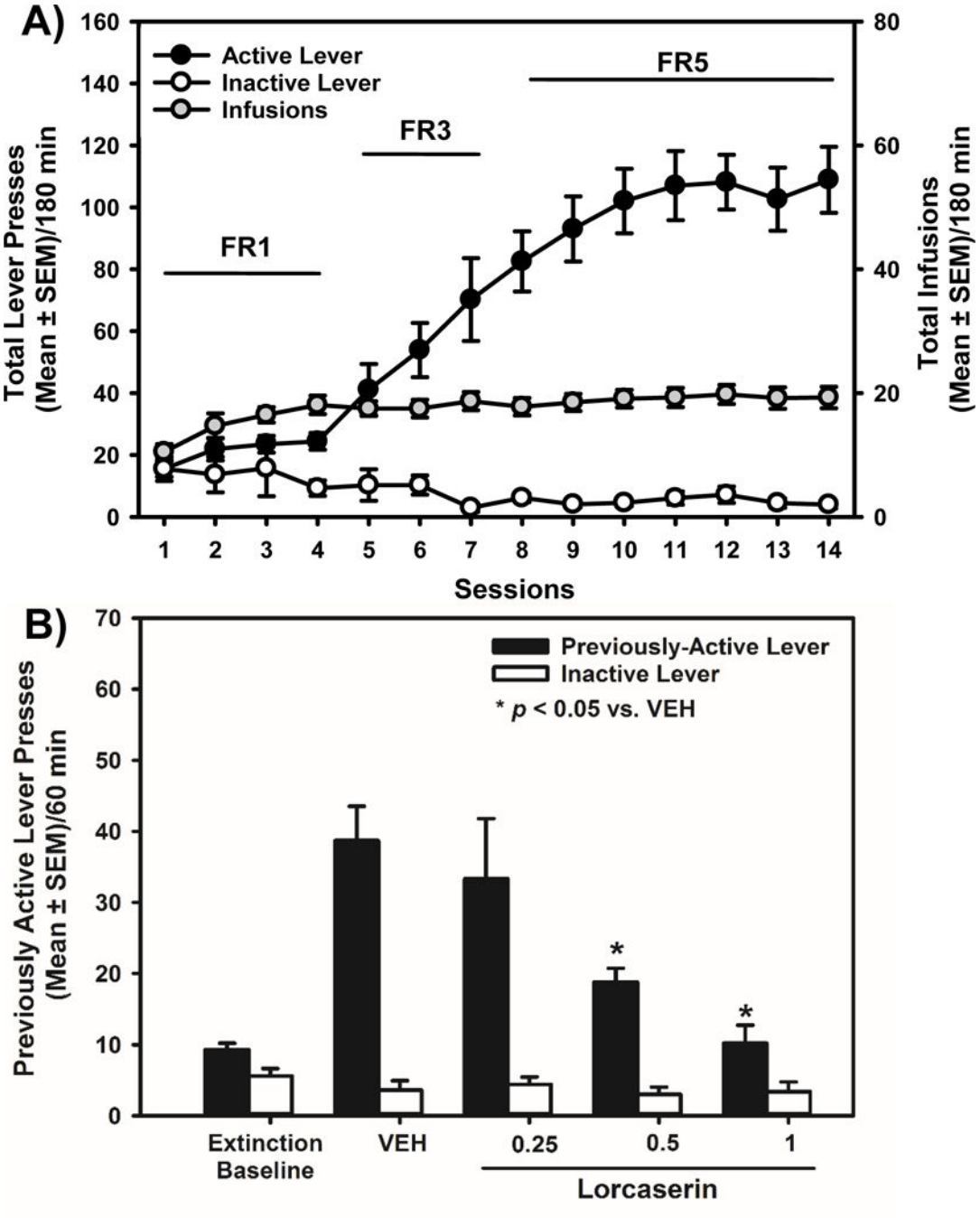

Figure 3. Lorcaserin suppresses cue reactivity in the extinction-reinstatement model

[A] Total presses (mean ± SEM) on the active (black circles) or inactive lever (white circles; left X-axis), and total number of oxycodone infusions obtained (gray circles; right X-axis) are presented for the acquisition of oxycodone self-administration. **[B]** The effects of lorcaserin (0.25, 0.5, 1 mg/kg) on previously active and inactive lever presses (mean ± SEM) following extinction training are presented. The "extinction baseline" was calculated as the mean total lever presses of all rats on the active (9.2 ± 2.9) or inactive lever (5.8 ± 1.1)

during the last 60-min extinction session. Lorcaserin (0.5 and 1 mg/kg) significantly reduced previously active lever presses relative to vehicle (*$p < 0.05$ vs. VEH).