A novel, short-acting kappa opioid receptor antagonist blocks the analgesic effects of U50,488 and attenuates symptoms of spontaneous oxycodone withdrawal in rats.

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OBJECTIVES

- Determine if CVL-354 is a short-acting (<24 hours) kappa opioid receptor antagonist.
- Determine if CVL-354 treatment reduces oxycodone-withdrawal induced somatic signs without suppressing locomotor activity or potentiating plasma corticosterone (stress biomarker).

CONCLUSIONS

- CVL-354 has KOR antagonist actions in thermal pain assays for at least 4 hours (but less than 24)
- CVL-354 reduces somatic withdrawal signs in a spontaneous oxycodone withdrawal model
- Lofexidine, but not CVL-354, reduces locomotion and elevates plasma corticosterone during spontaneous oxycodone withdrawal.
- **KOR antagonism may provide better overall efficacy for mitigation of opioid withdrawal symptoms than the current standard of care.**

Disclosures: GLS, PI, SD, SC, GG, SC are employees of Cerevel Therapeutics and may hold stock and/or stock options in the company. **MN, GC and EC** have nothing to disclose.

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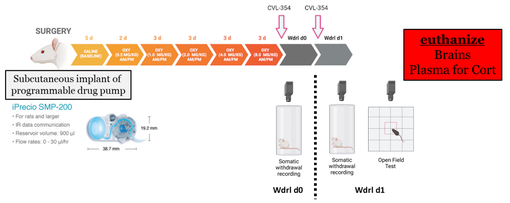
INTRODUCTION

A large body of preclinical evidence has demonstrated that the neuropeptide dynorphin (DYN), which acts at kappa opioid receptors (KOR), is a key player in opioid withdrawal. Chronic opioid exposure increases DYN and KOR activation and is thought to produce negative affective states including anhedonia, anxiety-like, and aversive behaviors. Importantly, KOR antagonism (KORA) has been shown to reduce opioid withdrawal signs and escalation of opioid self-administration in rodent models. However, KORA compounds used in these preclinical models (e.g., norBNI, JDTic) have extremely long (weeks) KOR antagonist actions. As such, the development of a selective and short-acting KOR antagonist has the therapeutic potential to facilitate discontinuation of opioid use with a pharmacological profile better suited for clinical development. CVL-354 is a potent, selective and short-acting KOR antagonist that was tested in a rat model of spontaneous oxycodone withdrawal.

METHODS

Spontaneous oxycodone withdrawal

Adult male Sprague Dawley rats were used for all experiments. Rats were subcutaneously implanted with iPRECIO minipumps (Alzet, model SMP 200) programmed to deliver an escalating dose regimen of oxycodone or saline 2x/day for 14 days, at the end of which, spontaneous opioid withdrawal signs emerged in oxycodone, but not saline, treated rats. Rats were administered CVL-354 (0.0, 0.1, 0.3, 1.0 mg/kg, SC) at 6-h (Wdrl d0) and 24-h (Wdrl d1) after cessation of drug delivery and somatic withdrawal signs including diarrhea, ptosis, wet dog shakes, teeth chattering, and body flattening were measured. Effects of CVL-354 and lofexidine on locomotor activity were measured using Open Field chambers (Med Associates) on Wdrl d1 to test for hyper- or hypo-locomotion—an undesired effect. Activity was digitally recorded and scored using DeepLabCut (Mathis et al., 2018). As a control for attenuation of spontaneous withdrawal signs, we administered the a2 noradrenergic agonist lofexidine (0.64 mg/kg) to separate rats. At the end of behavioral testing on Wdrl d1, rats were euthanized via decapitation to collect plasma for ELISA-based corticosterone analysis. All animal procedures approved by McLean Hospital IACUC protocol 2020N000106.



Thermal Pain Assays

Rats were treated with CVL-354 (0.0 – 1.0 mg/kg, SC) followed either 1, 4, or 24-h later by the KOR agonist, U50,488 (30 mg/kg, SC) and nociceptive responses were measured in the Tail Flick (TF) and Hot Plate (HP) thermal pain assays.

Statistical Analyses

Statistical analyses used were: One-way ANOVA (somatic withdrawal, corticosterone) and two-way ANOVA with repeated measures on time (open field test, tail flick and hot plate tests). Dunnett's post hoc tests comparing treatment to control groups were done when appropriate.

RESULTS

Figure 1

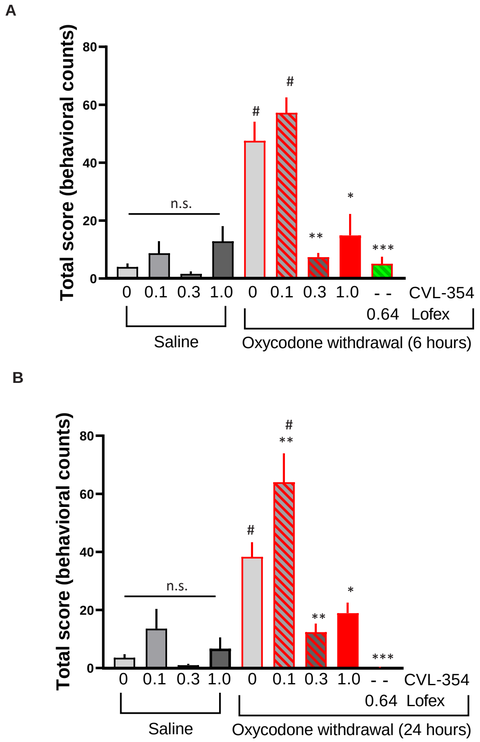


Figure 1. Effects of CVL-354 on total somatic withdrawal signs in oxycodone-dependent and non-dependent rats. Total withdrawal score was calculated by summing the behavioral counts for ptosis, wet dog shakes, teeth chattering, and flat posture. **A:** Data are recorded 6-h after the last subcutaneous oxycodone infusion. **B:** Data are recorded 24-h after the last subcutaneous oxycodone infusion. Total somatic withdrawal signs were significantly increased in the Oxycodone groups treated with vehicle and 0.1 mg/kg CVL-354 compared to saline + vehicle. CVL-354 significantly decreased total signs of somatic withdrawal at 0.3 mg/kg and 1 mg/kg doses. CVL-354 was dosed 30-min prior to recording signs of withdrawal. Data are the number of behavioral counts in the 30-min session. N= 7-19. *p<0.05 compared to Oxy + veh, **p<0.01 compared to Oxy + veh; ***p<0.001 compared to Oxy + veh; #p<0.01 compared to Saline + Veh.

Figure 2

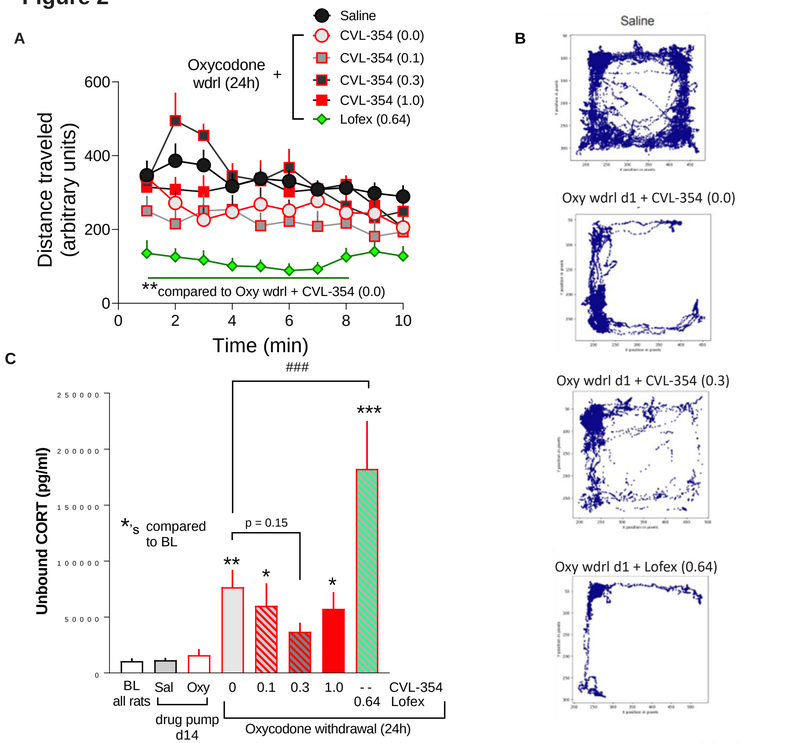


Figure 2: A: Locomotor activity: Rats on spontaneous oxycodone withdrawal day 1 (wdrl d1) treated with vehicle (CVL-354, 0.0mg/kg) showed qualitatively decreased distanced traveled relative to saline control rats (black circles), although CVL-354 did not significantly alter locomotor activity at any dose. Lofexidine (Lofex; 0.64 mg/kg) significantly and robustly decreased distance traveled on wdrl d1 relative to all groups, consistent with a sedative-like effect. N=7-11/Oxycodone + CVL-354/Lofex groups and N=22/Saline group. **p<0.01 comparing treatment to oxycodone wdrl + CVL-354 (0.0). **B**. Representative traces of Open Field locomotor activity using DeepLabCut analysis of digital recordings. Qualitatively, oxycodone-withdrawn rats (2nd trace) showed less overall activity and less activity in the center of the arena, indicative of anxiogenesis. Oxycodone-withdrawn rats treated with CVL-354 (0.3mg/kg; 3rd trace) showed recovery of overall and center locomotor activity. Lofex suppressed locomotor activity. **C:** Corticosterone (CORT) plasma levels in response to CVL-354 or Lofex treatment of rats during spontaneous oxycodone withdrawal. Blood draws were conducted at baseline (BL), on drug pump infusion d14, and after behavioral tests on wdrl d1. ELISAs were used to quantify unbound (free) CORT levels. Spontaneous oxycodone withdrawal (wdrl d1; grey bar, red outline) resulted in a significant elevation in CORT compared to BL. CVL-354 did not significantly decrease CORT levels compared to oxycodone withdrawal alone, but CORT levels after CVL-354 (0.3 mg/kg; dark grey with red stripes bar) were not significantly different from BL. Lofex caused a robust increase in CORT levels compared to BL as well as oxycodone withdrawal alone. N=6-13 for oxycodone + CVL-354 wdrl d1 groups, N=10 for oxycodone + Lofex wdrl d1 group. *p<0.05, **p<0.01 compared to BL. ###p<0.001 comparing groups under bracket.

Figure 3

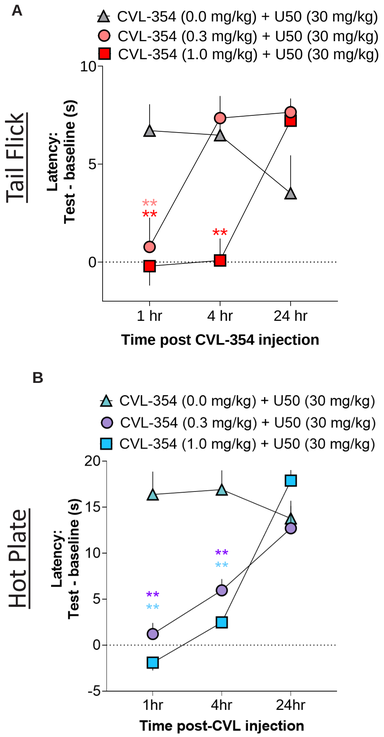


Figure 3: Time course of CVL-354-mediated blockade of U50,488 analgesia: CVL-354 is a short acting KOR antagonist. **A:** In the Tail Flick assay, both 0.3 and 1.0 mg/kg CVL-354 blocked analgesia at 1-h post-CVL, whereas only the 1.0 mg/kg CVL dose had an effect at the 4-h time point. **B:** In the Hot Plate assay, both CVL doses significantly reduced analgesia at 1 and 4 h. In neither assay did CVL-354 block U50,488's effects at 24 h. N=9/dose. h = hour. Latencies represent the time (s) it took each rat to flick its tail out of the focused light beam (tail flick) or lift/lick a hand paw off the hot plate floor. **P<0.01 compared to vehicle + U50 (30 mg/kg).