The effects of dual hypocretin/orexin receptor blockade on oxycodone seeking and dopamine neurotransmission in the nucleus accumbens

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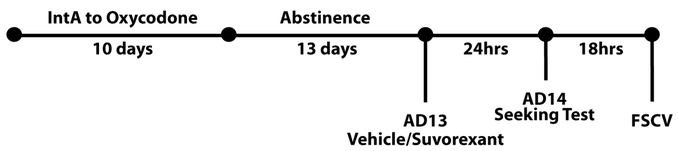
Introduction

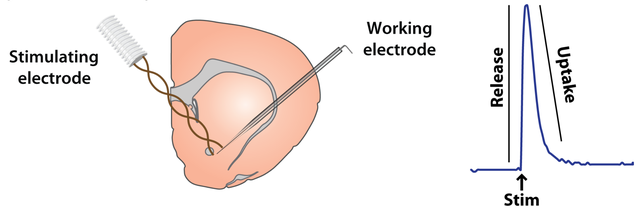
Opioid use disorder remains a pervasive public health issue, with prescription opioids, such as oxycodone, greatly contributing to the opioid crisis. A major barrier for treating opioid use disorder is the high prevalence of relapse during periods of drug abstinence. Drug craving has been shown to persist throughout abstinence and has been identified as a major contributing factor for relapse. The neural processes that contribute to drug craving remain incompletely understood. However, we recently showed that abstinence from oxycodone is associated with disrupted dopamine uptake rate in the nucleus accumbens. Despite these advances, and the availability of opioid-based medications for opioid use disorder, there has not been significant progress in curbing the opioid epidemic. Consequently, identifying novel pharmacotherapeutic targets remains a major research objective. The hypocretin/orexin (hypocretin) system is an attractive candidate for treating opioid use disorder due to substantial evidence that hypocretins influence motivation for opioids, and dopamine transmission. To examine the effect of a duel hypocretin receptor antagonist, Suvorexant, on opioid craving, rats were trained to self-administer oxycodone with a subsequent craving/seeking test following a period of abstinence. Rats were then sacrificed the day following the seeking test to assess the effects of Suvorexant on dopamine dynamics in the nucleus accumbens.

Methods

Female and male rats were trained to self-administer oxycodone under an intermittent access (IntA) schedule of reinforcement for 10 days. Following self-administration, rats underwent a forced abstinence period for 14 days. Rats were treated with Suvorexant (30 mg/kg) or vehicle on abstinence day (AD) 13 and were tested for oxycodone seeking on AD14. On AD15, we conducted fast scan cyclic voltammetry (FSCV) to measure dopamine dynamics following Suvorexant treatment.

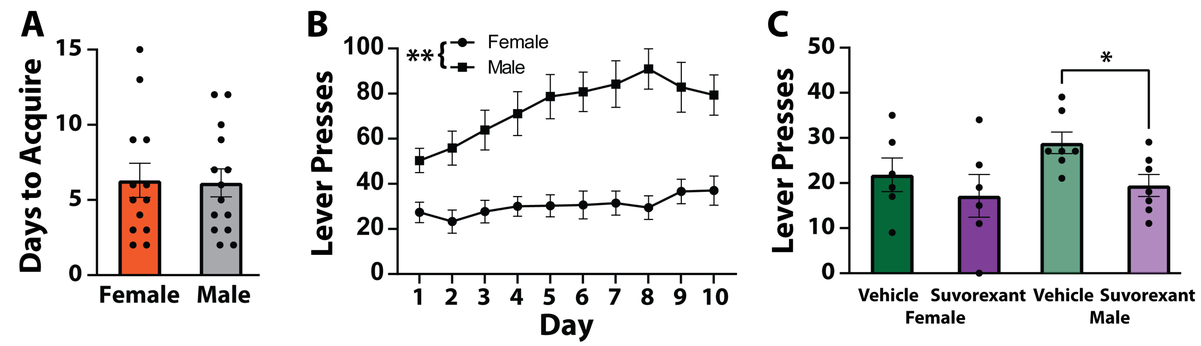


For FSCV, rats were sacrificed and 400 µm thick striatal slices were retrieved. Recording and stimulating electrodes were placed into the nucleus accumbens core, and an electrical pulse was delivered to elicit dopamine release. Baseline measures were recorded for dopamine release and uptake. Following baseline recordings, oxycodone was bath applied at increasing concentrations to determine the effect of oxycodone on dopamine transmission.



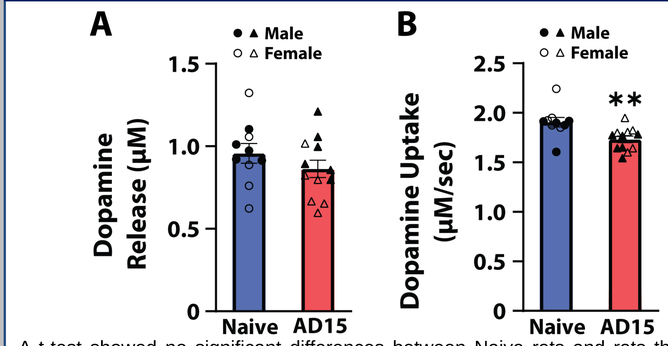
Left; schematic of a brain slice depicting a stimulating and recording electrode in the nucleus accumbens core. Right; Example trace showing stimulated dopamine release and uptake.

1. Hypocretin receptor blockade reduces oxycodone seeking



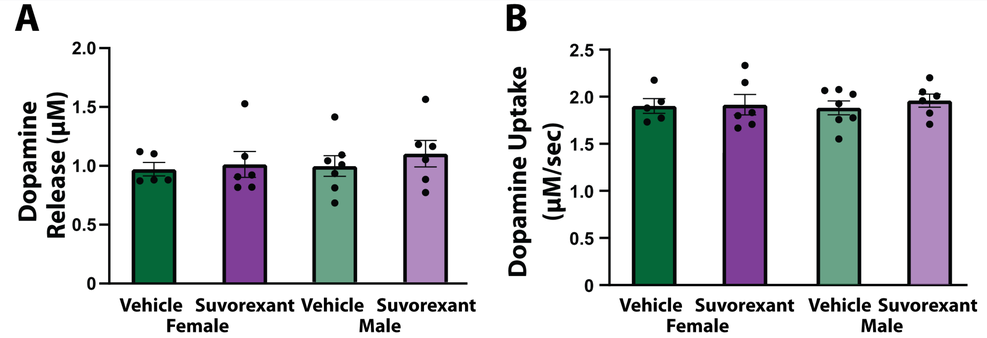
(A) Rats reliably acquire oxycodone self-administration. **(B)** A 2-way ANOVA showed a significant effect of sex on oxycodone intake [F(1,21)=21.92, p<0.01]. **(C)** A 2-way ANOVA showed a significant effect of treatment on cue-induced seeking [F(1,26)=320.94, p=0.046]. Sidak post hoc tests revealed a significant difference between vehicle and suvorexant in males (p=0.049).

2. Abstinence from oxycodone reduced dopamine uptake rate



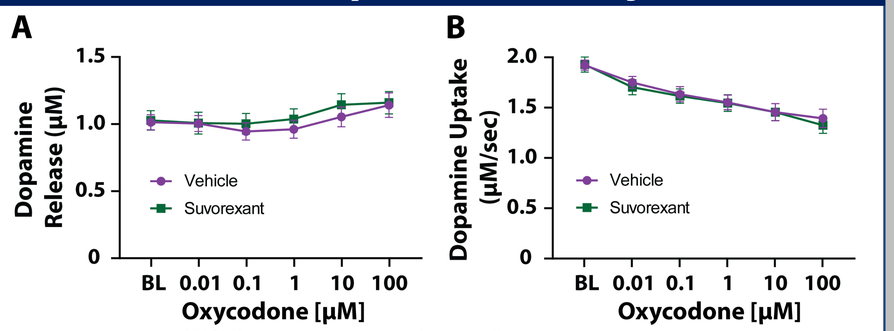
A t-test showed no significant differences between Naive rats and rats that self-administered oxycodone on AD15 for **(A)** dopamine release [t(20)=1.173, p=0.255], but there was a significant difference for **(B)** dopamine uptake [t(20)=3.025, p=0.0067].

3. Hypocretin receptor blockade did not affect baseline dopamine dynamics



2-way ANOVAs showed no effect of treatment on **(A)** dopamine release [F(1,24)=0.555, p=0.465] and **(B)** dopamine uptake [F(1, 24)=0.273, p=0.607].

4. Hypocretin receptor blockade did not affect response to oxycodone



Repeated measures ANOVAs showed no significant difference between treatment groups across concentrations of oxycodone for **(A)** dopamine release [F(1,18)=0.1878, p=0.670] and **(B)** dopamine uptake [F(1,18)=0.0489, p=0.827].

Summary and Future Directions

Suvorexant 24 hours prior to seeking tests reduced oxycodone seeking, but this effect was significant only for males

Suvorexant did not influence dopamine release and uptake at baseline

Suvorexant did not alter dopamine responses to oxycodone

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