Inhibition of Orexin-1 Receptors Attenuates Morphine-associated reward and underlying neurobiological alterations

Koly FA, Dao C and Perrotti LI.

Department of Psychology, The University of Texas at Arlington, Arlington, TX

Introduction

- Over 15 million people worldwide struggle with Substance use disorder(SUD).
- Morphine activates orexin neurons in the lateral hypothalamus (LH).
- OrxR1 plays a key role in regulating drug - seeking behavior.
- Orexin projections to dopamine-rich areas like the VTA and NAc influence drug-seeking behaviors.
- Blocking OrxR1 with SB-334867 can decrease dopamine release in LH.
- Most research has focused on males, making it essential to study these mechanisms in females.

Objective

Investigate how the lateral hypothalamus (LH) orexin system influences morphine-associated reward using a Pavlovian conditioned place preference (CPP) paradigm in male and female rats.

Materials & Method

Animals

Subjects: 18 Long Evans rats (6 males, 12 females)

Experimental Groups

Morphine Group (Control) (n = 12)

Treatment Group (Morphine + SB-334867) (n = 6)

Drugs and Doses

Morphine: 10 mg/kg, subcutaneous (SC) injection

SB-334867 (Orexin-1 receptor antagonist): 30 mg/kg, intraperitoneal (IP) injection

Saline: 0.1 ml/kg, subcutaneous (SC) injection

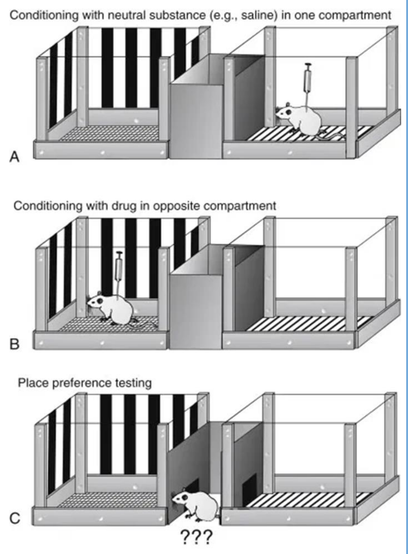
Conditioned Place Preference (CPP)

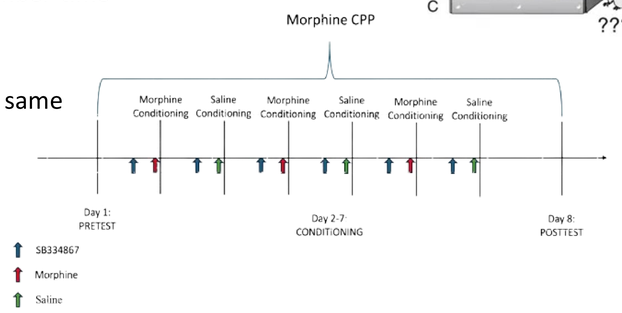
Assess the conditioned rewarding properties of drugs of abuse.

CPP score = Time spent in drug chamber-time spent in control chamber

Double-Label IHC

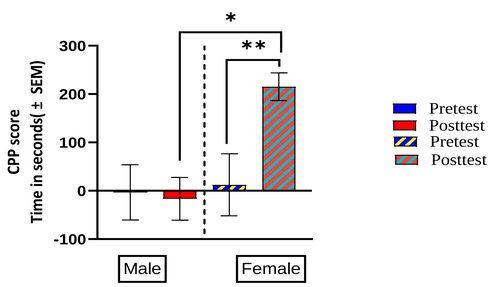
Co labeling of C-Fos & Orexin in the same cells of the LH region.





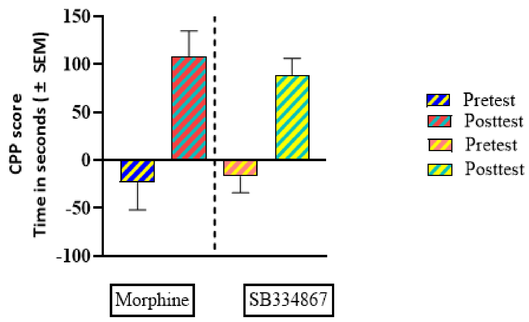
Results

Fig: 1. Development of Morphine CPP in female rats.



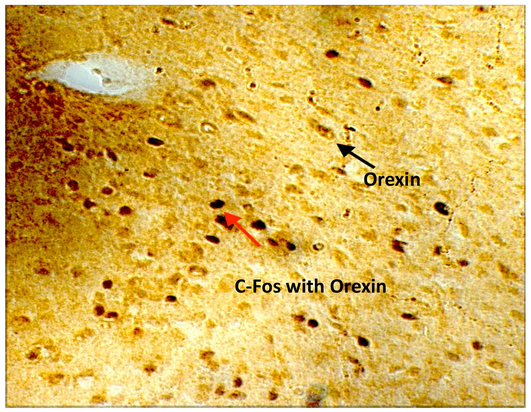
* *p*=.001, * *p*=.007

Fig:2. Effect of SB-334867 treatment on Morphine CPP in female rats.



(n =06)

Fig:3. Example image of C-fos & orexin co-labeling.



Summary

- Female rats developed a preference for the morphine-associated environment.
- In contrast, male rats did not show morphine preference.
- The OrxR1 antagonist SB334867 tended to reduce morphine CPP in female.

Limitations

- Male rats have slower morphine metabolism, leading to prolonged drug retention (Baker et al., 2002)
- Extended exposure could increase aversive effects, overshadowing rewarding experiences.
- Hormonal variations (e.g., estrogen) can influence drug response.
- Environmental condition can affect behavior and influence CPP.

Future Directions

- Add more rats to both the control and treatment groups to improve statistical power.
- Reduce morphine dose to 5 mg/kg for male rats to better explore dose-dependent effects on CPP.
- Administer the OrxR1 antagonist directly into the LH to investigate its localized effect on reward modulation.

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