The Role of the Estrous Cycle and Gonadal Hormones on Heroin and Sucrose Intake

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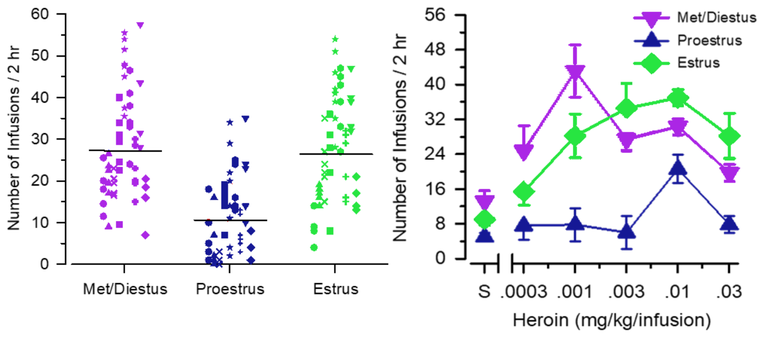
Introduction

Previously (Lacy et al 2016), we have shown that heroin intake decreases during the proestrus phase of the estrous cycle in female rats, and these decreases are maintained across a 100-fold dose effect curve.



The purpose of the present study was:

1) To examine the effects of the gonadal hormones estradiol and progesterone on heroin self-administration
2) To determine if proestrus-induced decreases in responding extended to a non-drug reinforcer

Methods

General Methods:
Female Long-Evans rats were trained to self-administer heroin on an FR1 schedule during daily 2-hr sessions. Estrous cycle was monitored via daily vaginal lavage 30-45 min prior to testing.

Experimental Methods:

1) In separate groups of gonadally intact female rats, heroin self administration (0.0075 mg/kg/inf) occurred for one estrous cycle. On subsequent proestrus days, we administered antagonists 30 min prior to testing:
   1) The estrogen-receptor antagonist, raloxifene
   2) The progesterone-receptor antagonist, mifepristone
   3) A combination of both receptor antagonists

2) In ovariectomized rats, we artificially replicated hormonal fluctuations during proestrus hormones via:
   1) Estradiol administration 22 hours prior to testing
   2) Progesterone administration 30 min prior to testing
   3) Both
   4) Vehicle

3) To determine the specificity of effects, we determined the effects of the estrous cycle on sucrose-maintained responding. Following heroin self-administration testing, rats were allowed to self-administer 45 mg sucrose pellets on an FR1 schedule.

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Results

Estrogen receptor antagonist blocks proestrus-induced decreases in heroin intake

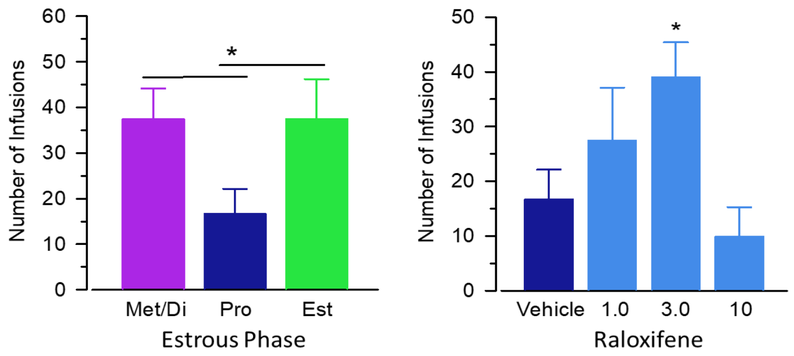

Fig. 1. Raloxifene blocks proestrus induced decreases in heroin self-administration. Left: Heroin self-administration across the estrous cycle. Right: Raloxifene (vehicle, 1.0, 3.0, 10.0 mg/kg; sc; 30 min prior to testing) effects on heroin self-administration.
Mean ± SEM. * $p < 0.05$.

Progesterone receptor antagonist fails to blocks proestrus-induced decreases in heroin intake

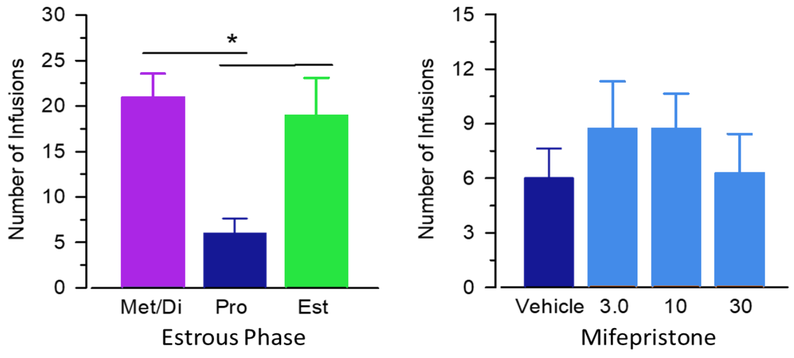

Fig. 2. Mifepristone fails to block proestrus induced decreases in heroin self-administration. Left: Heroin self-administration across the estrous cycle. Right: Mifepristone (vehicle, 3.0, 10.0, 30.0 mg/kg; sc; 30 min prior to testing) effects on heroin self-administration.
Mean ± SEM. * $p < 0.05$.

Estradiol but not progestogen is necessary for proestrus-induced decreases in heroin intake

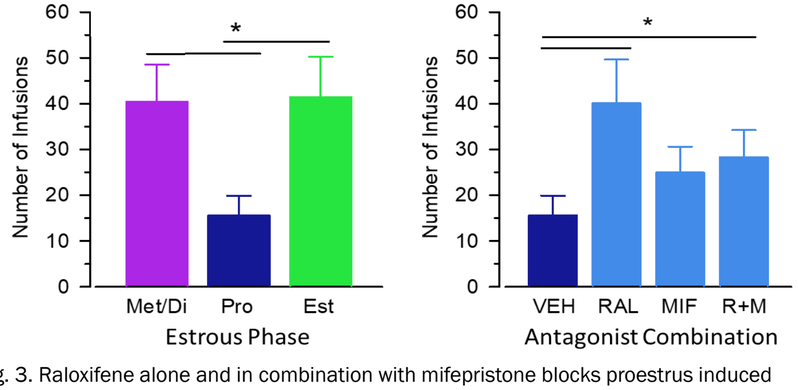

Fig. 3. Raloxifene alone and in combination with mifepristone blocks proestrus induced decreases in heroin self-administration. Left: Heroin self-administration across the estrous cycle. Right: Raloxifene (RAL; 3.0 mg/kg; sc), mifepristone (MIF; 10 mg/kg; sc), and their combination (R+M) effects on heroin self-administration.
Mean ± SEM. * $p < 0.05$.

Estradiol decreases heroin intake in ovariectomized rats

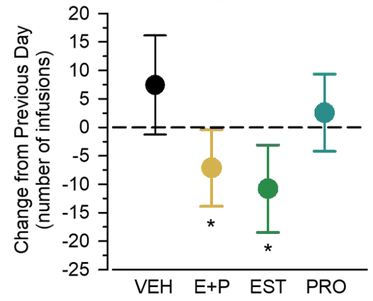

Fig. 4. Effects of hormonal artificial proestrus on reducing heroin self-administration from previous day. Vehicle (VEH), estradiol (0.005 mg, sc; 22 hours prior; EST), progesterone (0.125 mg, sc; 30 min prior; PRO), or both (E+P). Mean ± 95% CL.

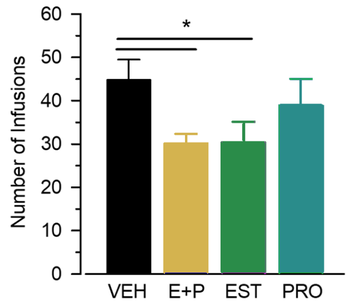

Fig. 5. Effects of hormonal artificial proestrus on reducing number of heroin infusions. Vehicle (VEH), estradiol (0.005 mg, sc; 22 hours prior; EST), progesterone (0.125 mg, sc; 30 min prior; PRO), or both (E+P). Mean ± SEM. * $p < 0.05$.

Proestrus-induced decreases in motivated behavior is specific to heroin

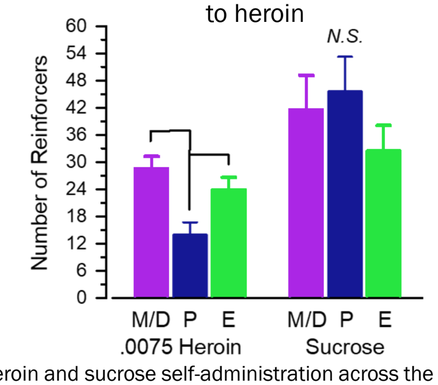

Fig. 6. Heroin and sucrose self-administration across the estrous cycle. Left: Number of heroin infusions. Right: Number of sucrose pellets delivered. Mean ± SEM. Brackets indicate significant differences ($p < 0.05$). N.S. indicates not significant ($p > 0.05$).

Conclusions

1) Estradiol, not progesterone, mediates the proestrus-induced decrease in heroin intake.
2) There may be therapeutic potential for estrogen-based medication for the treatment of opioid use disorder in women.

Acknowledgements

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