Effects of the Estrous Cycle and Ovarian Hormones on Opioid Intake

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RATIONALE

Female rats self-administer significantly less heroin during the proestrus phase compared to metestrus, diestrus, and estrus phases of the estrous cycle. During proestrus, both progesterone and estradiol levels reach their peaks. The purpose of this study was to:

- Replicate these findings in Long Evans (LE), Lewis (LEW) and Sprague-Dawley (SD) rats
- Determine the hormonal mechanisms mediating proestrus-induced decreases in heroin intake by testing the effects of exogenous estradiol and progesterone on heroin intake in ovariectomized female rats
- Determine whether chronic administration of exogenous hormones decreases opioid intake in intact female rats.

METHODS

General Methods: Female rats were trained to self-administer opioids on a FR1 schedule during daily 2-hour sessions.

- Exp. 1: Heroin (0.0025 or 0.0075 mg/kg/infusion) self-administration was measured in female Lewis, Sprague Dawley, and Long Evans rats.
  - Estrous cycle state was monitored daily via vaginal lavage 30-mins before testing.
- Exp. 2: OVX rats were chronically injected with: Estradiol (5 µg), Progesterone (0.125 mg) or, both.
  - Heroin self-administration was measured.
- Exp. 3: Intact female rats were chronically treated with vehicle, a low dose of estradiol, or a high dose of estradiol and heroin or remifentanil self-administration was measured.

RESULTS

Proestrus-induced Decreases in Heroin Intake Across Rat Strains

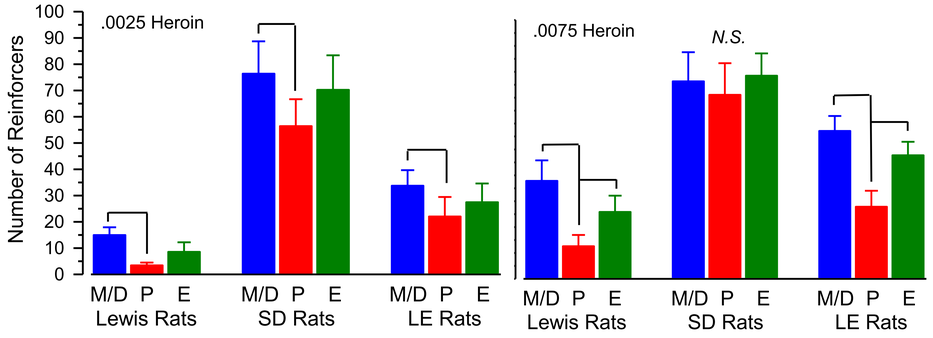

Fig 1: Heroin intake decreased significantly during proestrus in all three rat strains under at low dose condition (0.0025 mg/kg/infusion). Heroin intake decreased significantly in LEW and LE rats at a higher dose condition (0.0075 mg/kg/infusion). These effects were most robust in LE rats (Mean ± SEM. * p < 0.05).

Chronic Estradiol Reduces Heroin Intake in Ovariectomized Rats

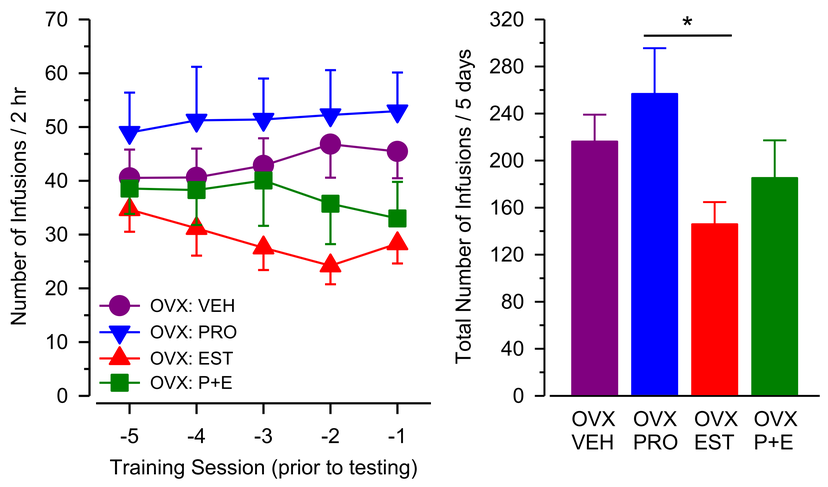

Fig 2: Estradiol (EST) reduces heroin intake in ovariectomized rats. Left: Rats were injected subcutaneously with VEH (peanut oil), EST (5 µg), PRO (0.125 mg), or P+E 30-mins prior to heroin self-administration 5 days prior to determination of the dose effect curve. Right: Number of infusions over 5 days (Mean ± SEM. * p < 0.05).

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(Jesharp@Davidson.edu).

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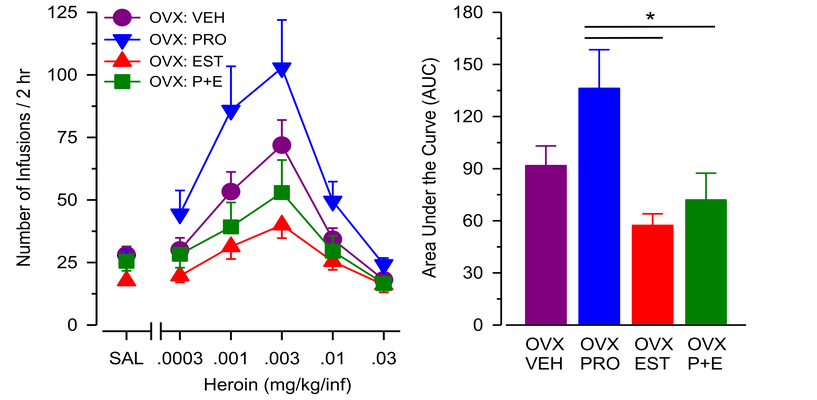

Fig 3: Estradiol, given alone or with progesterone, reduces heroin intake in ovariectomized rats. Left: Rats were injected subcutaneously with vehicle, EST (5 µg), PRO (0.125 mg), or P+E 30-mins prior to testing on a 100-fold heroin dose effect curve. Right: Area under the curve analysis (Mean ± SEM. * p < 0.05).

Chronic Estradiol Decreases Opioid Intake in Intact Female Rats

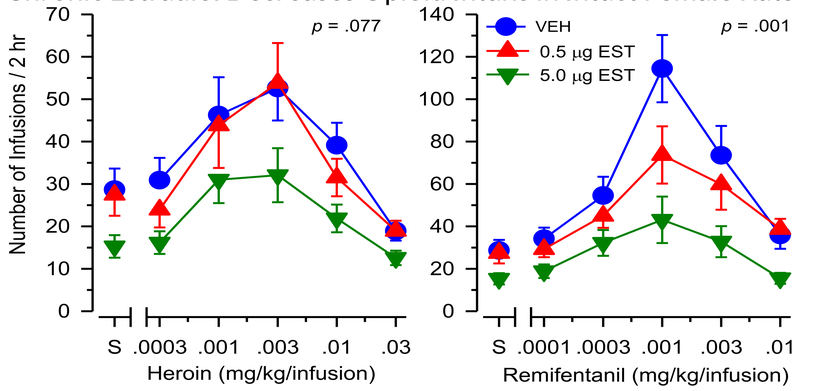

Fig 4: Estradiol non-significantly (p = 0.077) reduces heroin intake across a 100-fold dose effect curve (Left) and significantly (p = 0.001) reduces remifentanil intake across a 100-fold dose effect curve (Right) in intact female rats. Vehicle or estradiol (5 µg or 0.5 µg) injected subcutaneously 30-mins before testing (Mean ± SEM).

CONCLUSIONS

- Heroin intake decreases during proestrus across rat strains are likely mediated by estradiol and not progesterone.
- Chronic estradiol administration decreases opioid intake in intact female rats.
- Estrogen-based pharmacotherapy may represent a novel treatment approach for women with opioid use disorder.