Sex-specific dysfunction of cognitive and habit circuits underlying opioid self-administration

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Introduction

- Opioids are mainstays for clinical pain management despite known risk of dependence, and abuse even when used as prescribed.
- Biological sex is known to dictate drug-related behavior and susceptibility to neuropsychiatric disorders in humans, with females at heightened risk and often transitioning to uncontrollable drug use more rapidly than men.
- The prelimbic cortical region (PrL) of the medial prefrontal cortex (mPFC) plays a critical role in top-down inhibitory control of behavior. A prevailing view in the addiction field is that drug taking during the early stages of use is "goal directed" and controllable, however use becomes habitual in part due to reduced PFC control of behavior. However, empirical evidence for this with opioids is nonexistent.
- Deficits in cognitive flexibility produced by opioid self-administration in mice occurs more rapidly in females than in males and these deficits are driven by a hypoactive state in prelimbic region of the PFC (Anderson et al., 2021).
- ***Project Goal:*** Here, we outline how duration of opioid self-administration exposure and sex interact to impact PrL physiology and function and PrL control over drug. Secondarily we aim to determine whether changes in PrL control over behavior are unique to drug versus non-drug rewards.

Methods

Animals. Adult male and female wild-type C57BL/6 mice (postnatal day 68 ± 0.82 at self-administration onset) were bred in-house or commercially purchased (Jackson Laboratory).

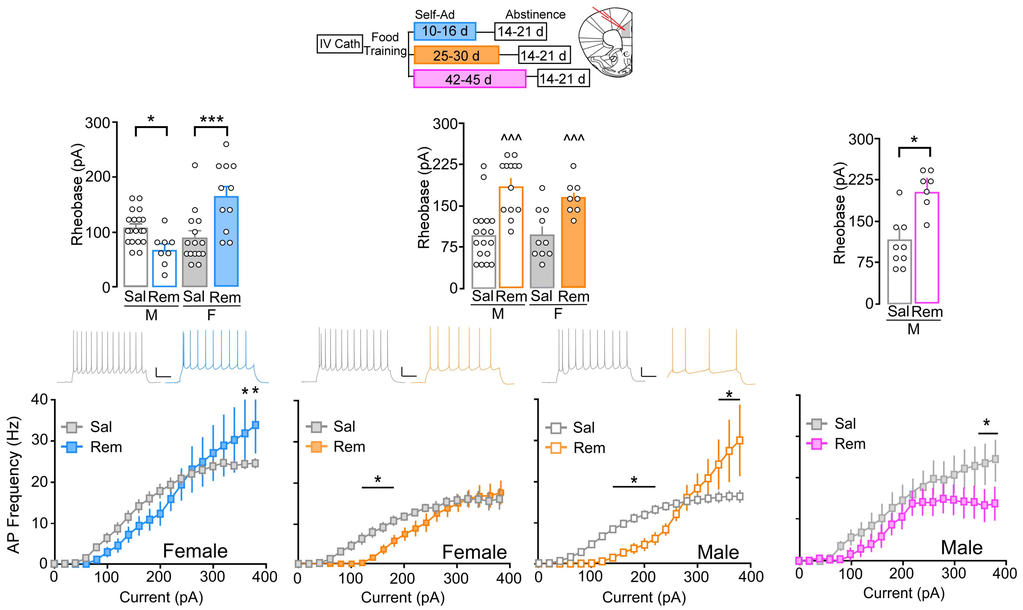
Remifentanil Self-Administration. Remifentanil (Rem; 0.005mg/kg/inf.), saline, or liquid Ensure® (50%) was administered on a FR1 schedule for 10-16, 25-30, or 42-45 days (>10 infusions/day). Following self-administration, mice were left undisturbed for 14-21 days.

In vivo DREADD manipulations. In attentional set-shift and self-administration studies, a subset of mice received a bilateral intracranial infusion of AAV8-CamKII-hm3d(Gq)-mcherry, AAV8-CamKII-hm3d(Gq)-mcherry or AAV8-CamKII-GFP/mcherry (UNC) into PrLC. Mice with viral infusions were given a saline intraperitoneal injection 30 minutes prior to testing in the visual cue test. On the day of the extradimensional shift, mice were given 1.5-2.0 mg/kg clozapine-n-oxide (CNO).

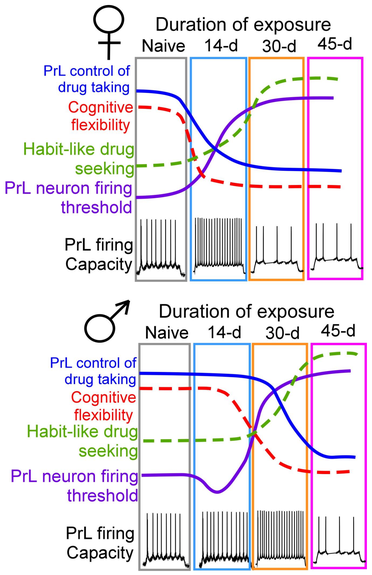
Slice electrophysiology. Whole-cell recordings were performed in L5/6 pyramidal neurons as previously described (Hearing et al., 2013; Anderson et al., 2019; Anderson et al., 2021b,c). Current-clamp recordings and voltage-clamp recordings of baclofen evoked currents were taken using a potassium gluconate internal solution, with recordings filtered at 2kHz and sampled at 5kHz. Postsynaptic current recordings were filtered at 2kHz and sampled at 20kHz performed with cesium methylsulfate internal at -72mV (EPSCs) and 0 mV (IPSCs) and 0.7 mM lidocaine added to the recording solution for mEPSCs/mIPSCs.

Data Analysis. Statistical analyses were performed using SigmaPlot with two-way ANOVA, ANOVA or RMP two-way ANOVA where appropriate.

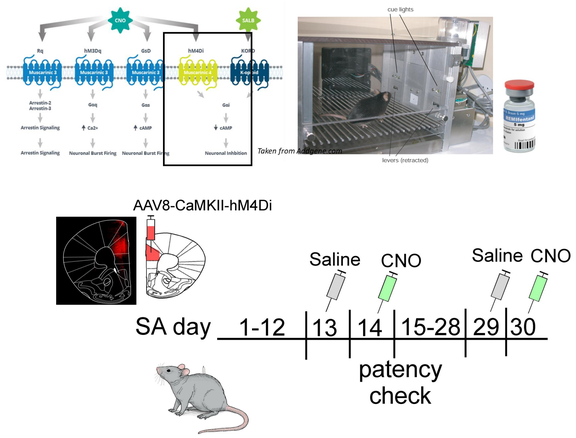
Supporting Data



Hypothesis/Working Model

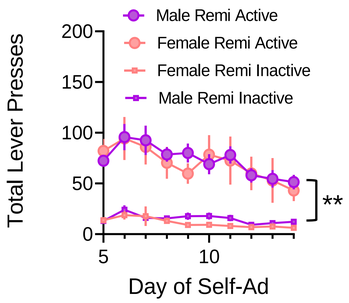


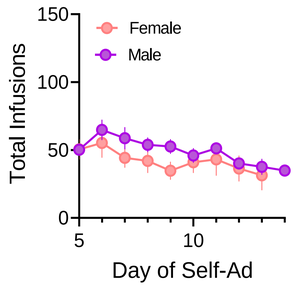
Experimental Design

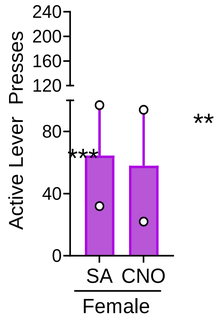


Results

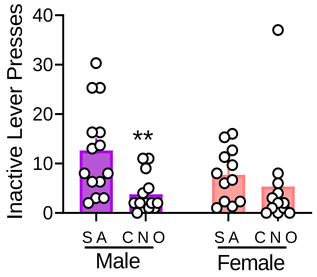
14-d Remifentanil Self-Administration

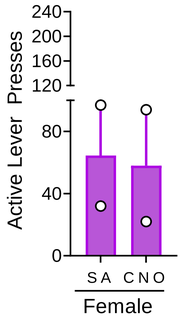




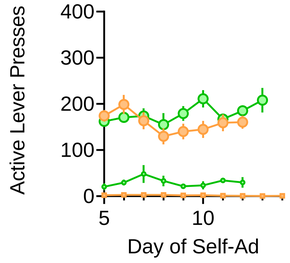


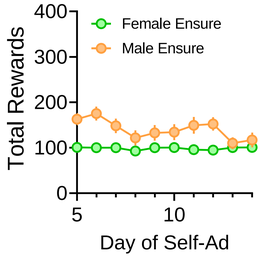
30-d Self-Administration

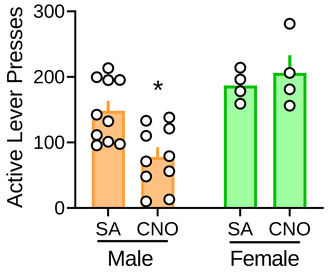


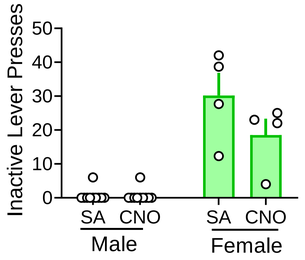


14-d Ensure Self-Administration









Summary/Conclusions

- Following 14-d of remifentanil self-administration, inhibition of the PrL in both males and females resulted in decreased drug intake.
- Preliminary data indicate that inhibition of the PrL after 30-d in females does not reduce drug intake indicating that control of drug seeking/drug taking becomes less reliant on prefrontal circuits.
- Inhibition of the PrL did not alter seeking behavior for a non-drug appetitive reward (Ensure). This suggests that the PrL either doesn't play a role in natural/food seeking behavior or that food seeking becomes more habitual on a shorter timescale.

Future Directions

- Extend timelines of remifentanil self-administration in males and females.
- Use DREADD approaches to inhibit habit-related neural circuits (anterior dorso-lateral striatum) to determine if behavioral control shifts to these brain regions.

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