Translational Investigation of Sex Differences in Alcohol Analgesic Efficacy: Comparison Across Preclinical and Clinical Domains

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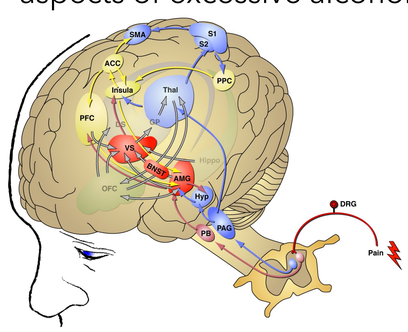
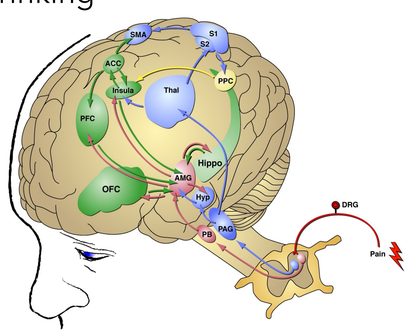
BACKGROUND

- Chronic pain affects over 220 million Americans and drives excessive alcohol use and dependence
- Alcohol is an effective analgesic in both chronic pain patients and people with alcohol use disorder
- Phosphorylation of glutamate (Glu) and γ-aminobutyric acid (GABA) receptors, and the intracellular signaling molecule ERK, have been implicated in chronic alcohol use
- Corticolimbic brain regions, such as the central amygdala (CeA) and the insular cortex, contribute to the motivational aspects of excessive alcohol drinking



Interaction w/ Extended Amygdala
"Nociceptive" Amygdala
Transition to Alcohol Use Disorder



Interaction w/ Cortical Circuitry
Pain-Related Negative Affect
Compulsive Alcohol Seeking

How much bodily pain have you had during the past 4 weeks?	
None	100
Very Mild	80
Mild	60
Moderate	40
Severe	20
Very Severe	0

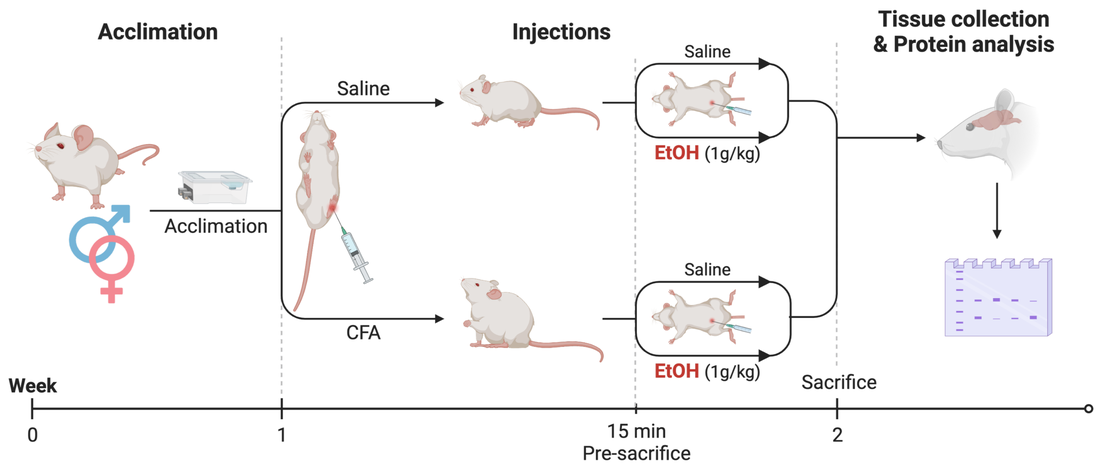
During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	
Not at All	100
Slightly	75
Moderately	50
Quite a Bit	25
Extremely	0

Note the inverted scale for SF-36:
lower scores represent more pain symptoms and pain interference

METHODS

Goals:

1. **Identify pain ratings following recent alcohol consumption in persons living with HIV (PLWH)**
2. **Investigate sex differences in corticolimbic neuroadaptations associated with persistent inflammatory pain and acute alcohol use in rats**

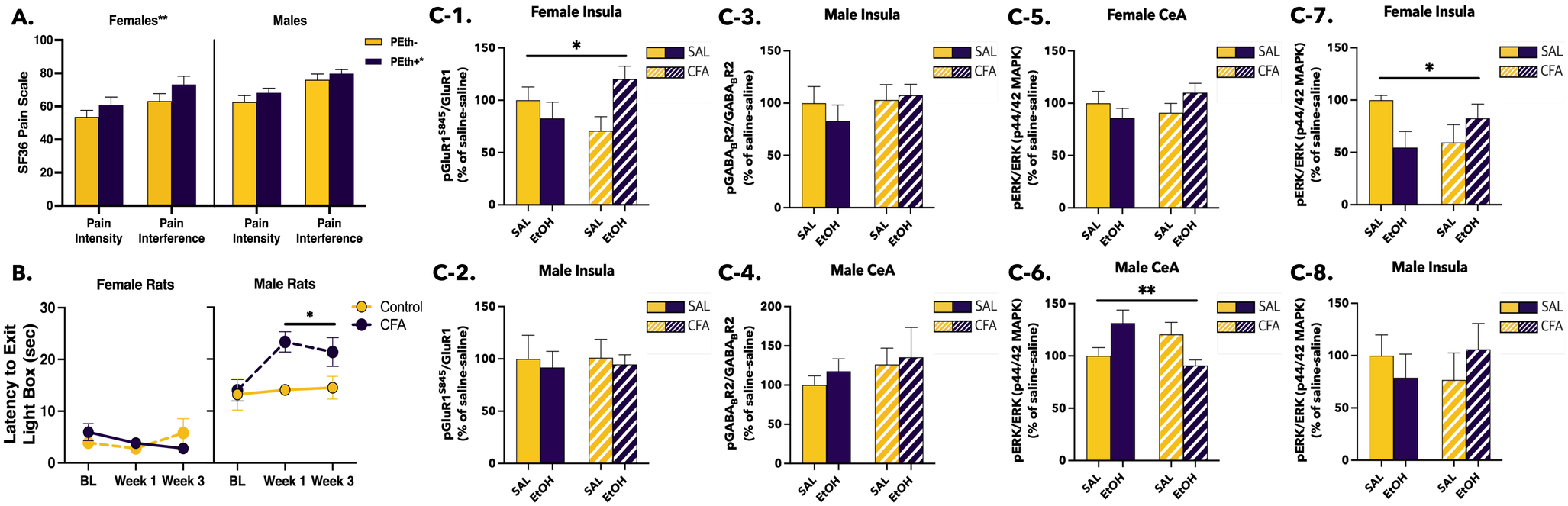


Subjects: Adult female & male (n=9-10/sex/group) Wistar rats
Chronic Inflammatory Pain: 150 µL subcutaneous 50% Complete Freund's Adjuvant (CFA) or saline (control) into left hind paw
Acute Alcohol: 15% w/v intraperitoneal ethanol (1.0 g/kg) administered in a Latin Square design

- 1.0 g/kg chosen to represent analgesic dose of alcohol and mimic human levels of binge drinking (≥ 0.08 g/dL)

Alcohol Differentially Alters Brain Nociceptive Systems of Male and Female Rats in Chronic Pain

RECENT ALCOHOL USE IMPROVES PAIN SYMPTOMS AND INTERFERENCE IN PLWH & FEMALES REPORT MORE PAIN COMPARED TO MALES
ACUTE ALCOHOL ALTERS CeA ERK PHOSPHORYLATION IN MALE RATS AND INSULA GLUTAMATE & ERK PHOSPHORYLATION IN FEMALE RATS



CONCLUSIONS

1. PLWH with recent alcohol use reported less pain and pain interference on the SF-36 Pain Symptom and Interference Scale compared to PLWH without recent alcohol use in both females and males. However, female PLWH reported more pain intensity and pain interference than male PLWH.
2. Acute alcohol administration increases ERK phosphorylation in male rats not experiencing chronic pain but decreases it in the CeA of male rats experiencing chronic pain, suggesting the CeA may contribute to the anti-nociceptive effects of acute alcohol.
3. Acute alcohol administration decreases glutamate and ERK phosphorylation in female rats not experiencing chronic pain but increases it in the insula of female rats experiencing chronic pain, suggesting the insula may be involved in mediating sex differences in nociception symptoms and avoidance in rats.

A. There was a significant main effect of alcohol to decrease pain symptoms and interference in PLWH with recent alcohol use (PEth+) compared to PLWH without recent alcohol use (PEth-) ($p = 0.0180$), and female PLWH experienced more pain intensity and interference compared to male PLWH ($p = 0.0014$).
B. There was a significant effect of chronic inflammatory pain increasing pain-avoidance behavior in male rats ($p = 0.0259$) but not in female rats ($p = 0.9727$).
C. There was a significant interaction such that alcohol decreases phosphorylation of GluR1^{S845} in the insula of female rats without chronic pain and increases it in the insula of female rats with chronic pain (**C-1**; $p = 0.0231$). There was a significant interaction such that alcohol increases ERK phosphorylation in the CeA of male rats without chronic pain and decreases it in the CeA of males with chronic pain (**C-6**; $p = 0.0066$) but decreases it in the insula of female rats without chronic pain and increases it in the insula of female rats with chronic pain (**C-7**; $p = 0.0195$). There was no significant interaction of alcohol to alter $GABA_BR2$ phosphorylation in male insula and CeA (**C-3,4**; $p = 0.4579$, 0.8693), GluR1^{S845} phosphorylation in male insula (**C-2**; $p = 0.9582$), and phosphorylation of ERK in male insula (**C-8**; $p = 0.2931$) and female CeA (**C-5**; $p = 0.0990$).
Data are represented as mean ± SEM.
N = 5-6/group.

Acknowledgements

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