Pharmacological Evaluation of the Ghrelin System as a Target for Binge Drinking

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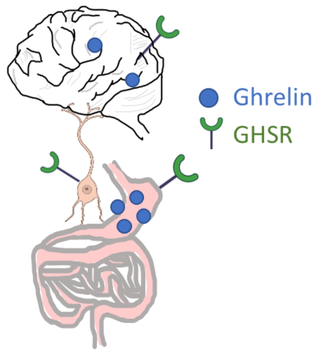
INTRODUCTION

- Ghrelin is a peptide hormone produced primarily in the stomach
- Its receptor, GHSR, is expressed in the brain and in the periphery
- The ghrelin system may be a novel target for the treatment of alcohol use disorder (AUD)
- Novel GHSR blockers and an anti-ghrelin vaccine have recently been developed
- LEAP2 is a recently-discovered peptide that functions as an endogenous antagonist of GHSR



OBJECTIVE

- Examine effects of an anti-ghrelin vaccine and six GHSR blockers JMV 2959, PF-5190457, PF-6870961, HM-04, YIL 781, and LEAP2 on binge-like drinking in male and female mice
- Hypothesis: blockade of the ghrelin system will decrease alcohol intake in both sexes

METHODS

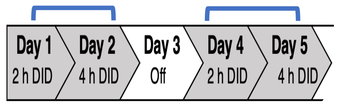
Drinking in the Dark (DID)

4-6 weeks baseline drinking

Drug testing prior to 4-hour sessions

During Dark Phase

During Dark Phase



*For IP and ICV administration of GHSR blocker, all drugs had 60 min pretreatment time except JMV 2959 (20 min)

Drinking solution: 20% v/v sweetened alcohol, 20% v/v alcohol, or non-alcohol sweet solution

Intraperitoneal (IP) administration

4-5 treatment days: Latin Square design for 4-5 doses, within subjects

Intracerebroventricular (ICV) administration

Counterbalanced design, within subjects

20 or 60 min* prior to DID session → DID

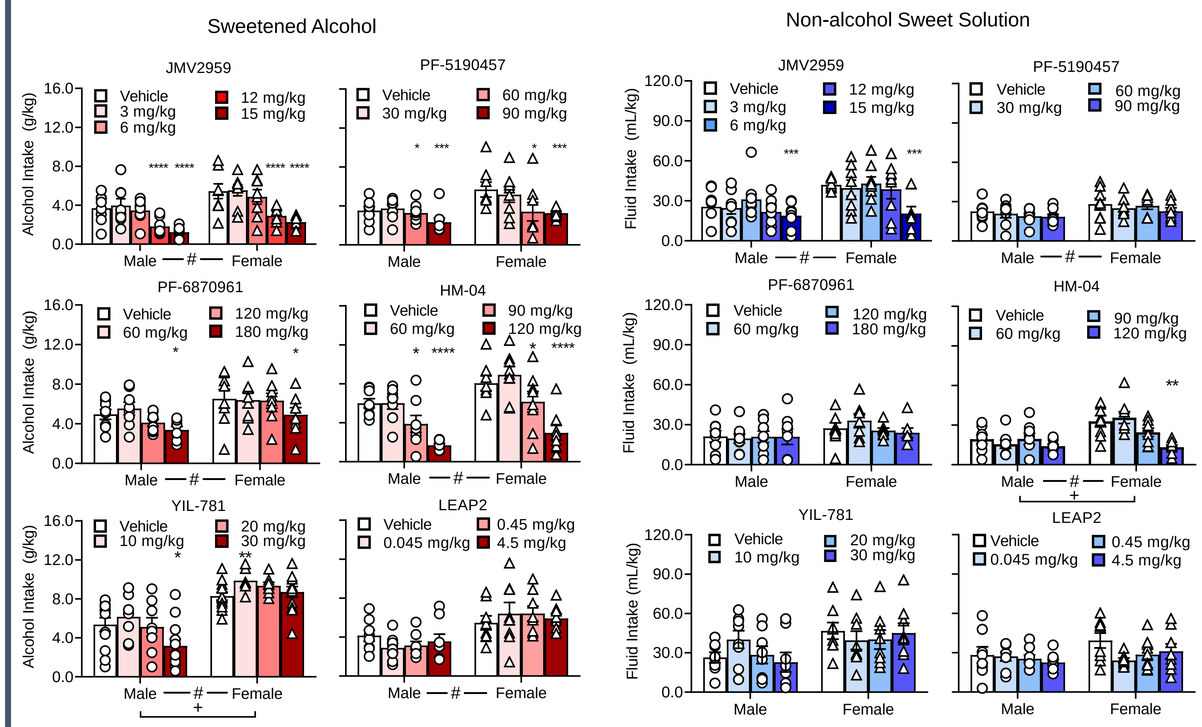
Anti-ghrelin vaccination

Administered three doses of anti-ghrelin vaccine over a 30-day period of DID via IP injection

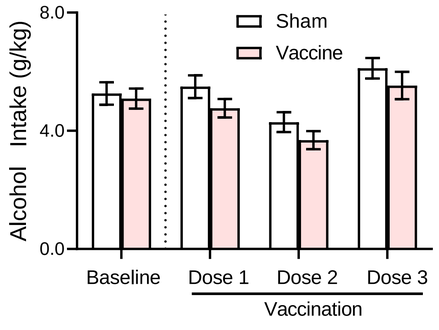
RESULTS

Binge-like Drinking (4 h) in C57Bl6/J Male and Female Mice

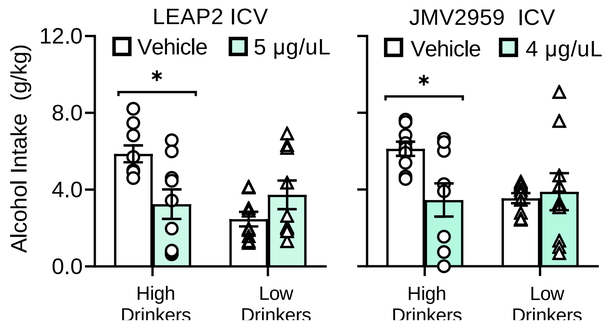
Systemic Administration of GHSR Blockers (IP)



Anti-ghrelin Vaccination (IP)



Central Administration of GHSR Blockers (ICV)



For systemic administration: $p < 0.05$, ***$p < 0.001$, ***$p < 0.001$, ****$p < 0.0001$, difference in intake between vehicle and drug; #$p < 0.05$, difference between male and female intake regardless of drug; +$p < 0.05$, interaction between sex and dose Vehicle: $n = 16$ (8M, 8F) Drug: $n = 16$ (8M, 8F). For vaccine administration: $n = 49$ (25M, 24F) Sham: $n = 27$ Vaccine: $n = 22$. For ICV administration: $n = 18$ (10M, 8F).

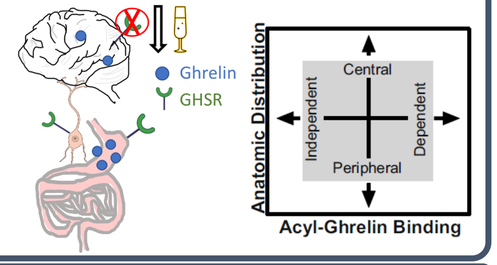
SUMMARY

Ghrelin Receptor Blocker (systemic administration)	Sex	Effect on Sweetened Alcohol	Effect on Unsweetened Alcohol (data not shown)	Effect on Non-alcohol Sweet
JMV 2959 (antagonist)	M	* ↓	↓	↓
	F	* ↓	↔	↓
PF-5190457 (inverse agonist)	M	↓	↓	↔
	F	↓	↓	↔
PF-6870961 (antagonist)	M	↓	↔	↔
	F	↓	↔	↔
HM-04 (antagonist)	M	↓	↓	↔
	F	↓	↓	↓
YIL 781 (antagonist)	M	↓	↔	↔
	F	↔	↔	↔
LEAP-2 (antagonist)	M	* ↔	↔	↔
	F	* ↔	↔	↔

*ICV Administration decreased intake

CONCLUSIONS

- GHSR blockade reduces binge-like alcohol drinking in male and female mice, and the effect appears to involve centrally-expressed GHSR
- GHSR blockade may have translational potential as a treatment for AUD
- Peripherally-circulating ghrelin may not be the main driving force behind binge-like alcohol drinking
- This work has translational potential as PF-5190457 is the first GHSR inverse agonist to advance to clinical development



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