Sex differences in the role of CNIH3 in opioid seeking

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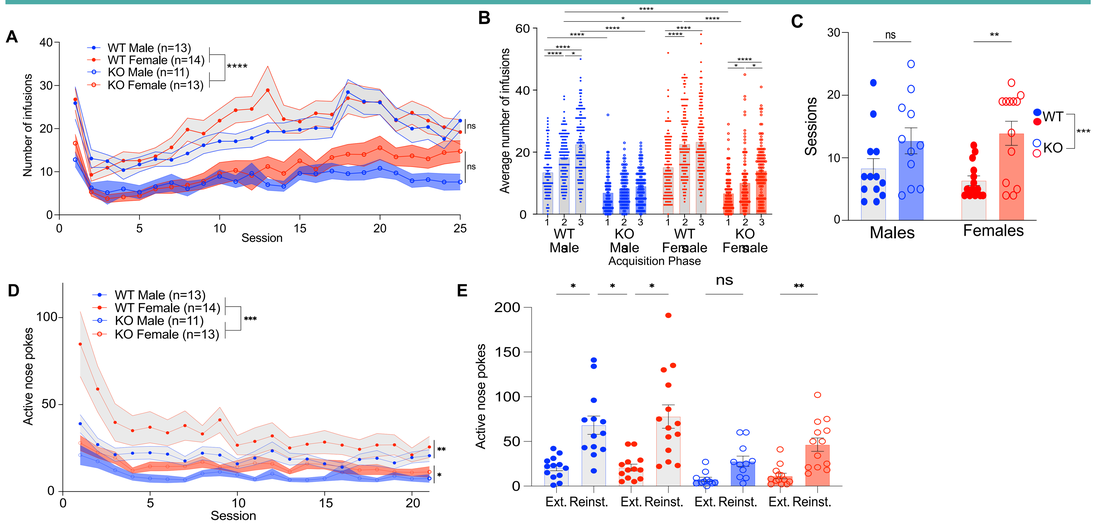
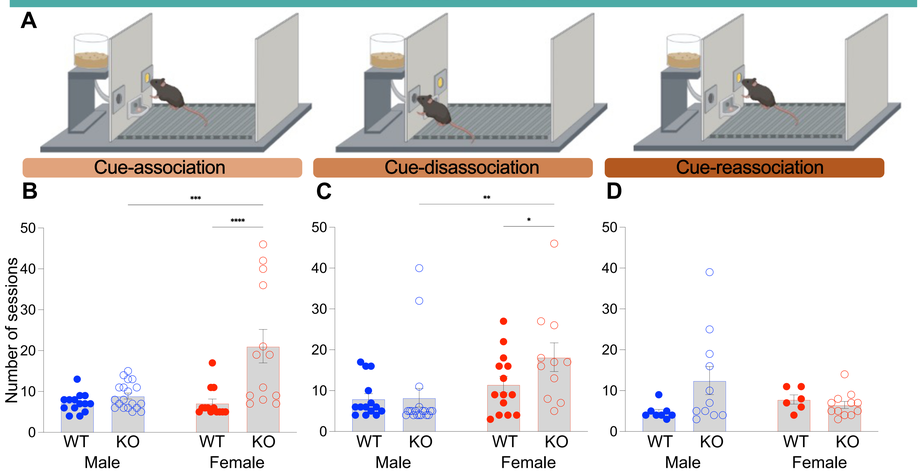
Introduction

Opioid overdose deaths have rapidly increased due largely to potent synthetic opioids such as fentanyl, and the persistence of opioid-cue associations that potentiate relapse. Recent evidence has highlighted the necessity of the dorsal hippocampus (dHPC) in opioid-cue association. Cornichon homolog-3 (CNIH3) is an AMPA receptor (AMPAR) auxiliary protein involved in AMPAR trafficking and signaling, and is highly expressed in the dHPC. AMPARs are key components of hippocampal synaptic plasticity and opioid-cue formation. Human genomic studies have proposed a role of CNIH3 in opioid dependence risk, especially in women, but the role of CNIH3 in opioid-cue association and opioid seeking is unknown. Here we assess how CNIH3 affects fentanyl and natural reward consumption, cue-reward association, and cognitive flexibility in mice, in addition to dHPC AMPAR subunit composition following intravenous self-administration.

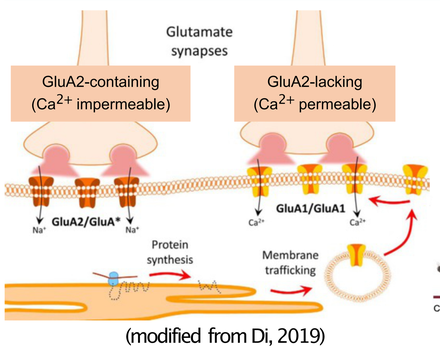
CNIH3 KO affects fentanyl IVSA acquisition, extinction, reinstatement



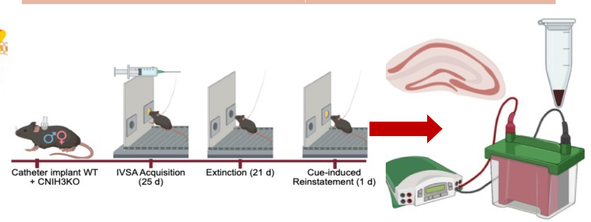
CNIH3 KO affects sucrose self-administration and cognitive flexibility in female mice

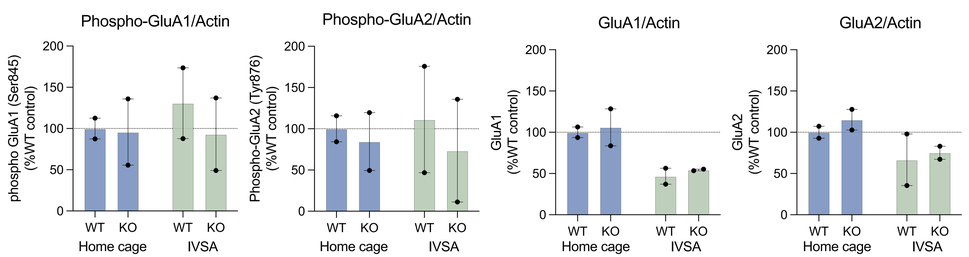


CNIH3 KO may alter AMPAR activation in the dorsal hippocampus following reinstatement



Phosphorylation site	Effect
↑ Phospho-GluA1 (Ser845)	↑ Receptor insertion
↑ Phospho-GluA2 (Tyr876)	↑ GluA2-containing receptor internalization





Conclusions

- CNIH3 KO impairs acquisition of fentanyl IVSA in female mice and prevents increased fentanyl consumption in males over time.
- CNIH3 KO reduces drug-seeking during extinction and dampens drug-seeking during cue-induced reinstatement in male mice.
- CNIH3 KO impairs acquisition of sucrose self-administration and cue disassociation in female but not male mice.
- Preliminary data suggests that after forced abstinence, CNIH3 KO may not affect AMPAR subunit composition, but may blunt reinstatement-induced AMPAR activation

Funding

NIH National Institute on Drug Abuse

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