Quantification and genetic mapping of oxycodone self-administration behaviors in nearly isogenic rat strains

Hao Chen[1], Shuangyin Leng[1], Sufiya Khanam[2], Megan K. Mulligan[2], Eva E. Redei[3]

1 Pharmacology, Addiction Science, and Toxicology, **2** Genetics, Genomics and Informatics, The University of Tennessee Health Science Center, Memphis, TN, **3** Department of Psychiatry and Behavioral Sciences, Feinberg School of Medicine, Northwestern University, Chicago, IL

Introduction

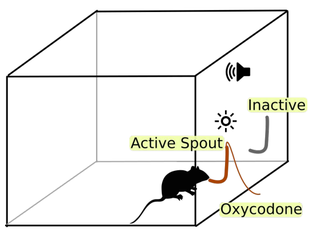
National overdose deaths from opioids continue to rise. Progression to opioid use disorder (OUD) is heritable but only a handful of gene variants have been identified by GWAS. To better understand genetic factors contributing to OUD, we characterized oral oxycodone (OXY) self-administration (SA) between WMI and WLI, two nearly isogenic rat strains, and identified QTLs for this behavior in their recombinant F2 progeny. Despite >99.99% genetic identity, these strains exhibit differences in OXY SA, creating an excellent opportunity to identify underlying gene variants.

Methods

Animals. Inbred WMI and WLI rats were generated by Dr. Eva Redei by selectively breeding from WKY rats based on the forced swim test. Breeders were transferred to the University of Tennessee Health Science Center (UTHSC) to establish a breeding colony. Both male and female adults, including F1 and F2 rats were used. Each rat was implanted with a radio-frequency identification (RFID) tag to facilitate individual tracking and identification throughout the study.

Oral Oxycodone Self-Administration. The self-administration of oral oxycodone was conducted using operant chambers (Med Associates) equipped with two lickometers. Licking on the active spout that met the requirement of a fixed ratio 5 (FR5) schedule resulted in the immediate delivery of 60 µl of oxycodone solution (concentration range: 0.025–0.1 mg/ml) to the tip of the spout. Concurrently, a visual cue was illuminated. A 20-second timeout period was enforced following each drug delivery, during which licks on the activespout were recorded but had no programmed consequences. Licks on the inactive spout were also recorded but did not result in any outcomes. Training began with five daily 1-hour sessions at an oxycodone concentration of 0.025 mg/ml.

Subsequent FR5 sessions were extended to 4 hours but were conducted on alternate days. The concentration of oxycodone was doubled every two sessions until it reached 0.1 mg/ml by session 8. This concentration was maintained for the remaining 10 sessions. Following the self-administration phase, extinction and cue reinstatement sessions were conducted. Throughout the experiment, food and water were provided ad libitum in the home cages.



Results

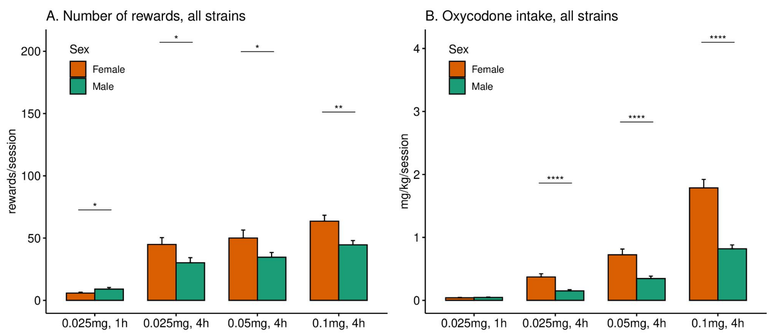


Figure 1. Sex difference in oxycodone reward and intake. Females received significantly more rewards (i.e. drops of oxycodone to the active spout) than males in all 4 hour sessions. The amount of intake (mg/kg/session) was also significantly higher in females than in males.

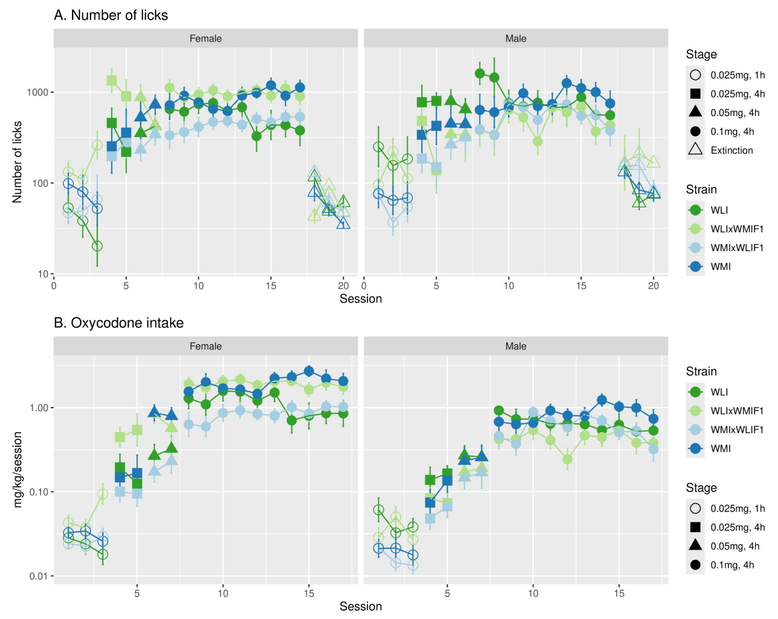


Figure 2. Oxycodone oral self-administration by session. Both female and male rats licked significantly more on the active than on the inactive spouts ($p<0.001$). The number of licks on the active spout also significantly increased acrosed self-administration stages ($p<0.001$). These data indicate that all rats increased voluntary oxycodone consumption across self-administration.

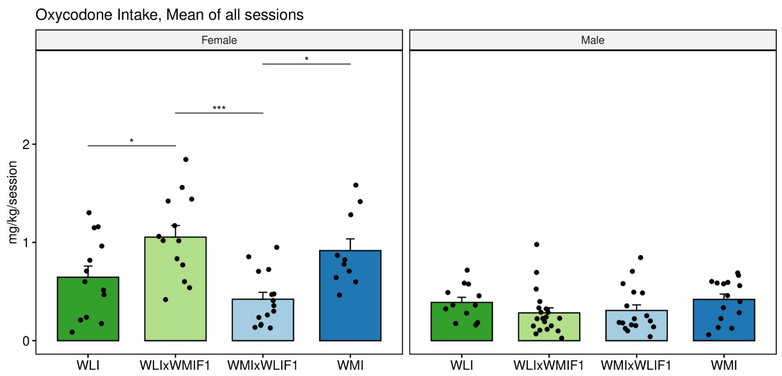


Figure 3. Parent of origin effect in oxycodone intake. In females F1s, WLIxWMIF1 (n=13, 1.1±0.14 mg/kg/session) consumed significantly more oxycodone compared to WMIxWLIF1 (n=15, 0.42±0.07 mg/kg/session, $p<0.001$). Oxycodone intake in in F1 males was not significantly different by strain (n=17-20).

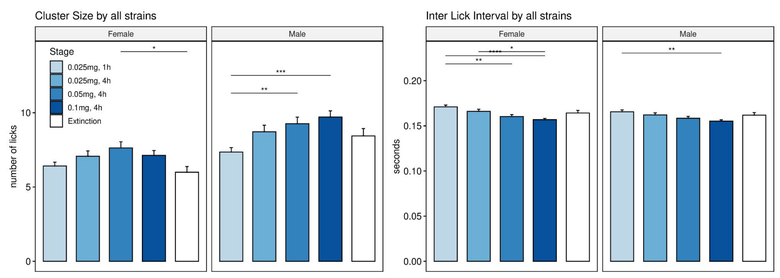


Figure 4. Sex differences in licking strategy. Larger cluster size and smaller interlick interval, in general, are indicative of higher hedonic value of oral rewards. In response to increasing oxycodone concentration, females responded primarily by reducing interlick interval (i.e. lick faster), males responded primarily by increasing cluster size (more licks in a bout).

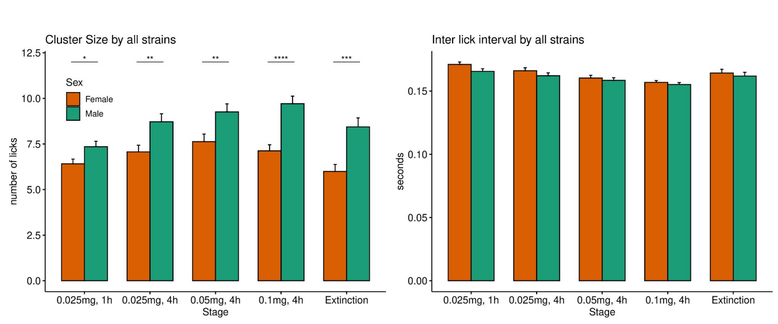


Figure 5. Sex differences in lick microstructure across different stages of oral oxycodone self-administration. Females had significantly smaller lick cluster across all stages of oral oxycodone self-administration than males. Interlick intervals are not significantly different between sexes.

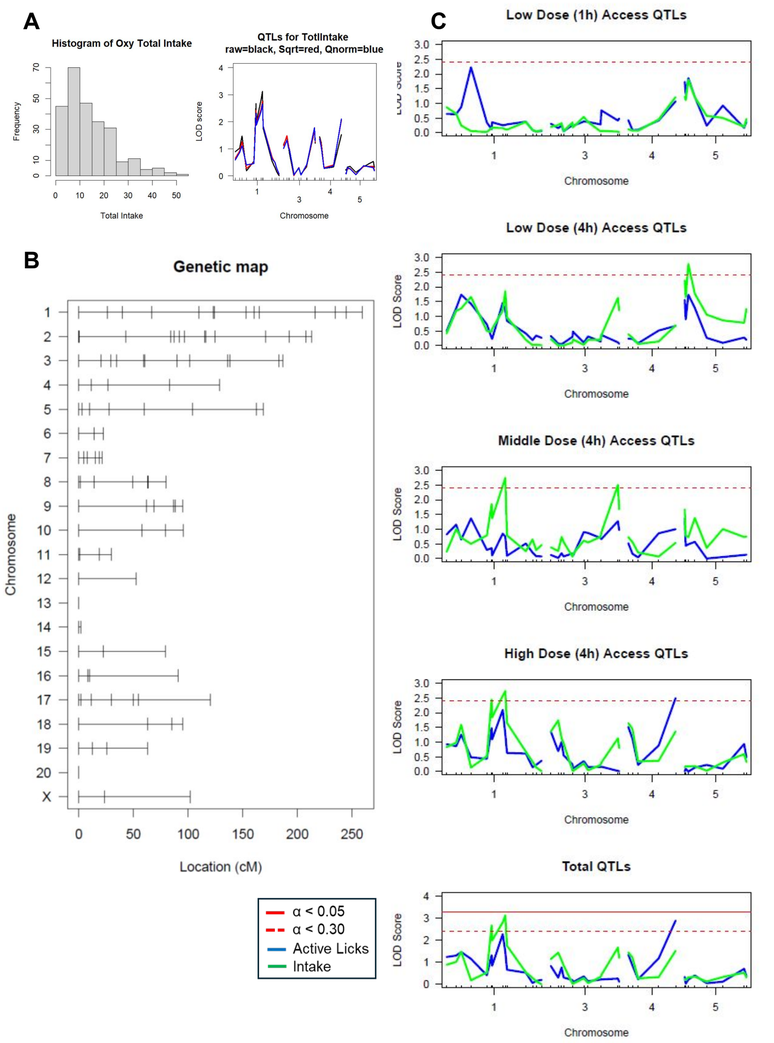


Figure 6. Preliminary Mapping Results. (A) Normalization does not improve mapping results. **(B)** Full RCC panel includes 117 markers and 269 F2 (pgm0: 69F, 66M; pgm1: 66F, 59M). **(C)** Genome-wide suggestive QTLs on Chrs 1,5 emerge at the lowest dose. QTLs transition to Chrs 1,3 at the middle dose and Chrs 1,4 at the high dose.

Summary

- **We found strong sex and strain effects on voluntary oxycodone intake in WMI/WLI inbred strains of rats**
- **We found a parent-of-origin effect on oxycodone intake in female F1 but not in males.**
- **Preliminary QTL mapping identified suggestive QTLs**

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