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

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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.

Rats were trained to self-administer OXY in operant chambers with two spouts, where one drop (60µl) of OXY was delivered after every five licks on the active spout. SA was conducted across 18 daily sessions, with OXY concentration increasing from 0.025 to 0.1 mg/ml and session length increasing from 1h to 4h. Lick microstructures were quantified for all sessions.

Across all sessions, female parent and F1 consumed more OXY than males (0.73±0.06 vs 0.34±0.03 mg/kg/session, mean±SE; $p < 0.001$), and WMI consumed more OXY than WLI (0.62±0.08 vs 0.51±0.07 mg/kg/session, p=0.001). There was a significant parent of origin effect on OXY intake in F1 females (WLIxWMIF1, n=13, 1.1±0.14 compared to the WMIxWLIF1, n=15, 0.42±0.07, p<0.001) but not in F1 males (n=17-20). Lick microstructure analysis showed rats increased cluster size and reduced interlick interval across the sessions, demonstrating increased subjective value of OXY.

202 F2 derived by reciprocal F1 crosses were genotyped at 212 markers and phenotyped for OXY SA followed by QTL mapping. Suggestive QTLs (LOD>2.6, α<0.3) for OXY SA at lower doses were identified on chromosomes 1, 5, and 15. At the highest dose, a suggestive QTL was identified on chromosome 4.