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Initial QTL Mapping of Oral Oxycodone Self-Administration in the Hybrid Rat Diversity Panel

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Most individuals affected in the national epidemic of oxycodone abuse began taking oral oxycodone by prescription. We studied vulnerability to oxycodone intake in a rat model of oral drug self-administration (SA) under a fixed ratio 5 schedule, where licking was used as the operant behavior. Rats were not water or food deprived. Training started with 0.025 mg/ml oxycodone, gradually increased to 0.1 mg/ml, and session length was extended from 1-h to 16-h, followed by extinction and reinstatement sessions. Females (49 strains) and males (45 strains) licked significantly more on the active spout compared to the inactive spout ($p<0.001$). The number of active licks were greater in females than males during 4-h and 16-h sessions ($p<0.001$ for all). Both sexes escalated intake during 16-h extended access vs 4-h sessions ($p<2e-16$). The heritability of active licks has a range from h2 of 0.22 to 0.59, while that for inactive licks ranged from 0.08, 0.34 at different stages of self-administration. Initial QTL mapping using GEMMA with LOCO identified several significant loci, among them, a region in Chr 1 between 159-172 Mb was associated with oxycodone intake at 0.025, 0.05 and and 0.1 mg/ml, 4h sessions, with max –log10(p) values of 6.1, 5.1 and 5.6, respectively. Potential candidate genes within this range include Cyp2r1 and Pde3b, both have strong cis-eQTL in the brain and are involved in vitamin D metabolism.

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