

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

Most individuals affected by the national epidemic of oxycodone abuse initiated use through oral prescriptions. We examined vulnerability to oxycodone intake using a rat model of oral self-administration (SA) under a fixed-ratio 5 schedule. Training commenced at 0.025 mg/ml oxycodone, increasing to 0.1 mg/ml, with session lengths extended from 1-h to 16-h, followed by extinction and reinstatement. Females (49 strains) and males (45 strains) exhibited significantly higher active spout licking compared to inactive spout licking ($p < 0.001$), with females consuming more than males during 4-h and 16-h sessions ($p < 0.001$). While both sexes increased intake during 16-h extended access, we identified "Augmenter" and "Non-Augmenter" strains based on their 16-h to 4-h intake ratio. Although 4-h intake means were equivalent between these groups, Augmenter strains exhibited a pronounced escalation in 16-h intake compared to Non-Augmenters ($p = 0.0005$). Lick microstructure analysis was employed to partition licks into "consumption" and "seeking" clusters to quantify hedonic impact and motivation. In Augmenter strains, the hedonic impact of consumption predicted subsequent drug seeking, whereas this association was absent in Non-Augmenters. The heritability (h^2) of active licks ranged from 0.22 to 0.59. Initial QTL mapping using GEMMA identified a significant locus on Chr 1 (159–172 Mb) associated with intake at multiple concentrations (max $-\log_{10}(p) = 6.1$). Candidate genes within this interval include *Cyp2r1* and *Pde3b*, which possess strong brain cis-eQTLs and are involved in vitamin D metabolism. Funding provided by NIH/NIDA U01DA053672.

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