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Sex and heredity are determinants of oral oxycodone self-administration in 36 Inbred Rat Strains: correlations with behavioral tests of anxiety and novelty-seeking

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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), since pharmacokinetics affect abuse potential. Females (33 inbred strains) and males (26 strains) obtained oxycodone at increasing concentrations in operant sessions (FR5; 1-16-h) followed by extinction and reinstatement. Active spout licks were greater in females than males during 4-h and 16-h sessions ($p<0.001$ for all). Across all stages of oxycodone SA, intake/session was greater in females ($p<0.001$). Both sexes escalated intake during 16-h extended access vs 4-h sessions ($p<2e-16$). Intake and active licks varied greatly by strain. The heritability (h2) of active licks/4-h at increasing oxycodone dose was larger in males (h2 females: 0.30-0.39 vs. males: 0.41-0.53). Under a progressive ratio schedule, breakpoints differed by strain ($p<2e-16$) and by sex in some strains ($p=0.018$). For cue-induced reinstatement, active licks were greater in females than males ($p<0.001$). Behavior in naive rats was assessed using elevated plus maze (EPM), open field (OF) and novel object interaction. (NOI) tests. EPM-defining traits were most commonly associated with SA in both sexes, whereas more OF and NOI traits were SA-associated in males. Overall, sex and heredity are major determinants of the motivation to take and seek oxycodone, which escalates during extended access. The correlation of EPM, a measure of anxiety, with multiple SA parameters indicates the influence of pleiotropic genes. Funding provided by NIH/NIDA U01DA053672 and U01DA047638.