Intravenous Cocaine Self-Administration in Inbred Mice: Genetic Correlation with Impulsivity and Genome-Wide Association Results

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Impulsivity is defined as trait-like proclivity to engage in reward pursuit or consumption behaviors, either due to unusually strong motivational urges to do so or to difficulty with reasoning about or controlling these behaviors. Impulsivity has long been associated with drug and alcohol use, abuse and dependence, and impulsivity and drug/alcohol use exhibit familial co-segregation, suggesting that they may be genetically correlated. We are engaged in a systematic effort to evaluate the heritability and co-heritability of impulse control behaviors (measured using an operant reversal learning test) and cocaine consumption (measured with an intravenous cocaine self-administration test) in separate cohorts of inbred mice drawn from a large genetic reference population – the hybrid mouse diversity panel. To date, we have conducted intravenous cocaine self-administration testing in adult male and female mice from more than 65 genetically distinct classical or recombinant-inbred mouse strains. All subjects were evaluated in 10, daily, 2-h testing sessions in which actuation of one lever elicited an intravenous infusion of cocaine (0.5 mg/kg/infusion) on a fixed-ratio-1 schedule of reinforcement. The majority of strains exhibit a clear pattern of cocaine-reinforced lever responding, but there are remarkable strain differences in stable, post-acquisition responding for cocaine. These strain differences appear to be genetically influenced, as the broad-sense heritability for levels of post-acquisition cocaine intake is 0.8-0.85. As hypothesized, levels of cocaine intake are modestly co-heritable with a measure of impulsive behavior derived from the reversal-learning test. To date, three, distinct genome-wide significant quantitative trait loci have been determined for cocaine intake, including a large-effect locus on chromosome 9. Literature-based evaluations suggest that *unc13c* (aka munc13-3), an interesting positional candidate known to regulate activity-dependent synaptic plasticity, endocannabinoid signaling and critical period-related neural plasticity, may be a positional candidate worthy of subsequent investigation. The effort to further identify specific genes co-regulating impulse control and drug self-administration may be enabled by the recent initiation of the Center for Systems Neurogenetics of Addiction, which is employing collaborative cross and diversity outcross mice in the integrated study of the same phenotypes (reversal learning and cocaine self-administration).