The Collaborative Cross as a tool for studying the genetics of addiction-related phenotypes

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Despite the high prevalence and substantial personal and societal burden of substance use disorders (SUDs), very few effective treatments currently exist. SUDs are complex and result from the action of many genes as well as environmental factors. Identifying specific genes that increase risk is critical to advance our understanding of these disorders and develop effective preventive measures and treatments. However, identifying human risk genes has been hampered by the genetic complexity of the disease, the difficulty of assessing environmental exposures and other methodological aspects of such studies. Rodent behavioral models have been developed to study aspects of SUDs and offer several advantages, including control of genetic background and the environment and access to brain tissue for genomic and mechanistic studies. The Collaborative Cross (CC) is an inbred mouse population that was designed to maximize phenotypic and genetic diversity and provide a platform on which to study complex systems genetics. As part of the Center for Systems Neurogenetics of Addiction (CSNA), we have identified two CC strains that are extremely divergent in their initial locomotor sensitivity to cocaine. We have characterized these lines for additional addiction related-behaviors and have identified a significant relationship between initial drug sensitivity and the reinforcing effects of psychostimulants. We have also explored the dopaminergic system, cocaine pharmacokinetics, and the hypothalamic pituitary adrenal axis as possible mechanisms. Finally, we took advantage of the unique genetics of the CC to conduct a mapping study aimed at identifying candidate genes that underlie the divergent cocaine phenotypes.

We present some of the first data on cocaine behaviors in the CC population. These data highlight the utility of the CC as a powerful tool for probing the specific genes and mechanisms that contribute to addiction-related behaviors and may ultimately be targeted for improved treatment and prevention.