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Systems genetics discovery of genetic, genomic, and gene-by-environment mechanisms driving substance use and sensation seeking

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Substance abuse is a critical public health issue with genetic and environmental causes. Sensation seeking is a multifaceted, heritable trait which predicts the development of substance use and abuse in humans, and similar phenomena have been observed in rodents. Genetic correlations among substance use and sensation seeking indicate shared biological mechanisms. Environmental enrichment attenuates both traits suggesting that effects occur through these shared mechanisms. The molecular and neurobiological mechanisms underlying these relationships remain elusive. We used a systems genetics approach in BXD recombinant inbred (RI) mice to identify (1) genetic mechanisms driving intravenous cocaine self-administration and (2) shared genetic mechanisms underlying operant sensation seeking and alcohol preference. To assess the feasibility of using the BXD RI panel to discover the mechanisms through which environmental factors influence the shared mechanisms underlying substance use and sensation seeking, we quantified the effects of environmental enrichment on operant sensation seeking, preference for a novel environment, and locomotion in a novel environment in the C57BL/6J and DBA/2J inbred strains, the founder strains of the BXD RI panel. We identified strain-dependent effects of housing condition on each of these distinct indexes of sensation seeking. Collectively, these data provide novel and, in some cases, shared biological mechanisms driving substance use and sensation seeking in the BXD RI mouse panel and provide evidence of genotype-dependent effects of environmental enrichment on sensation seeking traits in the BXD founder strains. This work was supported by NIDA K99 DA043573 to PED and NIDA R01 DA037927 to EJC.