Cocaine and cannabis: a joint dependence revealed by a longitudinal genetic study in mice

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Background/Rationale/Significance. To identify genetic pathways for addiction, we analyzed intravenous self-administration of cocaine or saline in a panel of 84 inbred and recombinant inbred mouse strains over 10 days. We integrated the behavior data with RNA-Seq data from the medial frontal cortex and nucleus accumbens from 41 strains.

Hypothesis. The self-administration of cocaine and saline showed distinct genetic bases. We maximized power to map loci for cocaine intake by using a linear mixed model to account for this longitudinal phenotype while correcting for population structure.

Results. A total of 15 unique significant loci were identified in the genome-wide association study (GWAS). A transcriptome-wide association study (TWAS) highlighted the Trpv2 ion channel as a key locus for cocaine self-administration from the GWAS. In addition, 17 genes supplementary to the GWAS were identified including Arhgef26, Slc18b1 and Slco5a1. We found numerous instances where alternate splice site selection or RNA editing altered transcript abundance.

Discussion. Our work emphasizes the importance of Trpv2, a known cannabinoid receptor, for the response to cocaine as well as identifying further relevant loci.