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Poster Submissions

Poster Title

HnRNP H1 regulates the stimulant and addictive properties of methamphetamine: Transcriptomic and spliceomic analyses uncover novel neurodevelopmental mechanisms

Authors and their Affiliation

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Please describe the extent of your work in this research

I am a fourth year PhD student leading this project under the mentorship of Dr. Camron Bryant. I have worked on TALENs gene-editing, behavioral analyses, and RNA-seq bioinformatic analyses, all of which are touched on in the abstract.

Abstract Submission

- **GSI-2015-abstract_NY_FINAL.docx**

Would you like your abstract to be considered for an oral presentation (students and post docs only)?

Yes

HnRNP H1 regulates the stimulant and addictive properties of methamphetamine: Transcriptomic and spliceomic analyses uncover novel neurodevelopmental mechanisms

Neema Yazdani[1,2], Eric Reed[3], Clarissa C. Parker[4,5], Ying Shen[6], Michael A. Guido[4], Loren A. Kole[4], Stacey L. Kirkpatrick[1], Jackie E. Lim[4], Greta Sokoloff[4,7], Riyan Cheng[4,8], W. Evan Johnson[6], Abraham A. Palmer[9], Camron D. Bryant[1]

Sensitivity to the locomotor stimulant effects of amphetamines is a heritable trait in mice that may aid in our understanding of the genetic and neurobiological basis of neuropsychiatric disorders involving perturbations in dopaminergic transmission. We previously used fine mapping with interval-specific B6J.D2J congenic lines to identify a 206 kb critical interval (**CI**) containing only two protein-coding genes, *Hnrnph1* and *Rufy1*, that was *necessary* for reduced methamphetamine (**MA**) sensitivity. More recently, we identified a B6J.D2J congenic line that possesses a mere 112 kb D2J interval that spans solely *Hnrnph1* and *Rufy1* genes. Phenotypic analysis of these congenics revealed that mice homozygous for this refined D2J interval also recapitulated the congenic phenotype (reduced locomotor activity after 2 mg/kg MA administration) hence deeming the CI *Hnrnph1* and *Rufy1* genes variants as not only *necessary* but *sufficient* for differential MA sensitivity. To determine the quantitative trait gene (**QTG**), we used transcription activator-like effector nucleases (**TALENs**) to induce small deletions in the first coding exon of *Rufy1* or *Hnrnph1*. Phenotypic analysis of replicate lines heterozygous for the *Hnrnph1* deletion (*Hnrnph1* hets) recapitulated the congenic phenotype while those heterozygous for the *Rufy1* deletion did not, thus identifying *Hnrnph1* as the QTG. With regard to addiction-like phenotypes, *Hnrnph1* hets displayed increased MA conditioned place preference (MA-CPP) relative to WT B6 littermates at the 2 mg/kg dose, and the inverse response at the 0.5 mg/kg dose, suggesting they are less sensitive to the rewarding properties of the drug. Because hnRNP H1 is an RNA-binding protein involved in alternative splicing of mRNA, we conducted splice variant analysis of RNA-seq data obtained from our B6J.D2J congenics using the Linear Models for Microarray Data (LIMMA) package, and then identified predicted exon targets that possessed hnRNP H1 binding motifs using RBPmap. Pathway analysis of target genes revealed “Nervous System Development and Function” as one of the top “Diseases and Biological Function” categories. Specifically, differential splicing of hnRNP H1 target genes is predicted to affect neuron quantity and development. These findings combined with transcriptomic analysis bolster our hypothesis that *Hnrnph1* regulates neurodevelopment of the mesocorticolimbic circuitry, thereby affecting dopaminergic neuron development and striatal signaling, and hence the stimulant and rewarding responses to amphetamines. These results will likely have widespread implications for understanding the genetic and neurobiological bases of disorders comprising perturbations in dopamine neurotransmission, including addiction, schizophrenia, ADHD, OCD, and Parkinson’s disease.

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