Submitter Name: Kasey Brida Submitted email: kbrida@uab.edu
PI Name: Jeremy Day PI email: jjday@uab.edu

Reelin regulates striatal excitability & cocaine reward

Kasey L. Brida[1], Emily Jorgensen[1] , Morgan Zipperly[1], Robert A. Phillips III[1], M. Natalie Davis[1], Kelsey Montgomery[2], Kristen R. Maynard[2], Keri Martinowich[2], & Jeremy J. Day[1]

[1]Department of Neurobiology, University of Alabama at Birmingham,
[2]Lieber Institute for Brain Development

Reelin is a large, secreted glycoprotein with a well-characterized role in brain development and links to numerous neuropsychiatric disorders. While Reelin is abundant in the adult striatum, Reelin's functional role in this brain region remains poorly characterized. Using a recently generated cellular atlas of the rat nucleus accumbens (NAc) following cocaine experience, we identified *Reln* mRNA as a marker of cocaine-responsive *Drd1*+ medium spiny neurons (MSNs). Here, we sought to define Reelin's role in striatal functions, and to determine its contribution to cocaine behavioral response. We designed a CRISPR sgRNA targeting the *Reln* promoter to enable repression of *Reln* transcription with CRISPR interference (CRISPRi). To assess if *Reln* serves as a passive marker of cocaine-sensitive cells or facilitates cocaine response, we performed conditioned place preference following targeted *Reln* knockdown in the NAc. Compared to non-targeting gRNA controls, *Reln* knockdown animals had no preference for the cocaine-paired chamber. To understand Reelin's role in regulating activity in the NAc, we used whole-cell patch clamp following *Reln* knockdown. While we saw no changes in passive membrane properties or action potential properties, cells lacking *Reln* exhibited decreased intrinsic excitability and an inability to maintain sustained firing. Single-nucleus RNA-sequencing of the NAc following *Reln* knockdown reveals changes in the expression of genes important for maintaining calcium homeostasis and provide direction for future pharmacological assays. Together, these results reveal a key role for Reelin in striatal function and cocaine reward. Ongoing studies are assessing Reelin's role in regulating MSN excitability and other aspects of cocaine-related cellular and behavioral adaptations.