Name: Kasey L. Brida
Email: kbrida@uab.edu
PI Name: Jeremy Day
PI email: jjday@uab.edu

Reelin protein marks cocaine-sensitive Drd1+ medium spiny neurons and modulates medium spiny neuron physiology and behavioral response to cocaine

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]Dept. of Neurobiology, University of Alabama at Birmingham;
[2]Lieber Institute for Brain Develop

Reelin is a large secreted glycoprotein with a well-characterized role in brain development and links to neuropsychiatric disorders. Using a cellular atlas of the rat nucleus accumbens (NAc) following cocaine experience, we identified Reln mRNA as a marker of cocaine-sensitive Drd1+ medium spiny neurons (MSNs). Single-molecule RNA fluorescence in situ hybridization for Reln and markers of striatal neuron subtypes demonstrates broad expression of Reln mRNA throughout the rat striatum, with enrichment in Drd1+ MSNs. These results were mirrored in postmortem human NAc tissue, where RELN mRNA was significantly more abundant in DRD1+ MSNs compared to other cell types (N=2 donors, 2 sections/donor, 1,156 cells). Next, we designed a CRISPR gRNA targeting the Reln promoter to enable Reln knockdown at both mRNA and protein level with CRISPR-interference (CRISPRi). Using whole-cell patch clamp in Reln knockdown NAc tissue, we find no alterations in passive membrane properties or action potential properties. However, a current step protocol shows severely decreased intrinsic excitability and inability to maintain sustained firing. Next, we find that targeted striatal knockdown of Reln via stereotactic delivery of Reln CRISPRi lentivirus expression vectors prevented formation of conditioned place preference for cocaine in Sprague-Dawley rats. Our results reveal a key role for Reelin in the electrophysiological properties of MSNs and behavioral adaptations to cocaine. Ongoing studies are combining pharmacological and genetic approaches to identify mechanisms of Reelin signaling and further explore Reelin's contribution to striatal function.