Name: Emily Jorgensen
PI Name: Jeremy Day

Email: ejorgens@uab.edu
PI Email: jjday@uab.edu

CRISPR-Based Manipulation of KCNQ Channel Subunits Reveals Unique Contributions to Striatal Neuron Activity

Emily Jorgensen, Jeremy Day

Department of Neurobiology, University of Alabama at Birmingham

KCNQ currents are important for controlling neuronal excitability, serving as a brake against hyperexcitable states in neurons. As such, changes in KCNQ channel expression and activity have been implicated in several neuropsychiatric disorders including substance abuse. While KCNQ subunits are encoded by a family of genes (Kcnq1 - Kcnq5) that form tetrameric channels, most prior work has used pharmacological approaches that lack genetic specificity. Additionally, little is known about subunit-specific contributions to reward circuitry and drug-seeking behaviors. To better understand the function of KCNQ channels in the striatum, we engineered CRISPR sgRNAs targeting the promoters for rat KCNQ subunit genes Kcnq2 and Kcnq3 to permit subunit-specific CRISPR activation/interference strategies. Our results demonstrate robust and bidirectional regulation of Kcnq2 and Kcnq3 in rat primary striatal neuron cultures, with potential cross-talk between Kcnq2 and Kcnq3 expression levels. To measure the role of KCNQ subunits on electrophysiological activity, we paired CRISPR manipulations with high-density multielectrode array recordings from striatal neurons. Notably, Kcnq3 knockdown selectively decreased action potential frequency, while knockdown increased frequency. Overexpression and knockdown of Kcnq2 increased bursts/min compared to non-targeting lacZ controls. These results supplement our previous findings of differential responses to pharmacological manipulation of KCNQ2/3 channels in the same cells, further demonstrating an important role for KCNQ channels in striatal cell function. Future studies will expand these results to determine how genetic manipulation of Kcnq2 and Kcnq3 affects striatal neuron responses to dopamine. These experiments will continue to provide insight into the physiological changes involved in substance use disorders.