Title: Understanding the synaptic interactions between the endocannabinoid system and ethanol: from mechanisms to behavior

Endocannabinoids and cannabinoid-1 (CB1) receptors have been implicated in the reinforcing effects of ethanol. Within the cortico-basal ganglia circuits, CB1 receptors are abundantly expressed on glutamatergic and GABAergic presynaptic terminals. It is likely that the cellular location of CB1 receptors within different brain areas and synapses may have differential functions involved in the reinforcers of addictive behaviors, such as ethanol. Neuronal processing of action learning and/or control is thought to involve the sensorimotor corticostriatal projections, neuronal inputs arising from primary motor cortex (M1) to the dorsolateral striatum as well as inputs to the external segment of the globus pallidus (GP) from the dorsolateral striatum, striatopallidal projections. Little is known about mechanisms by which ethanol interacts with endocannabinoid transmission, including which endocannabinoid type (AEA or 2-AG) is affected by ethanol at these terminals. Using brain slice photometry and a genetically encoded fluorescent G protein-coupled Receptor Activation Based endocannabinoid sensor ($GRAB_{eCB2.0}$) in M1-DLS (corticostriatal) and DLS-GP (striatopallidal) projections, we can begin to elucidate ethanol actions on endocannabinoid-CB1 receptor signaling with synapse-specificity. Acute ethanol exposure reduced $GRAB_{eCB2.0}$-mediated fluorescent transients detected at both corticostriatal and striatopallidal projections. Furthermore, targeted deletion of diacylglycerol lipase α (DAGLα), the 2-AG-synthesizing enzyme, in striatonigral medium spiny neurons altered ethanol-induced endocannabinoid transmission detected at corticostriatal projections and ethanol related behaviors. Using a multifaceted approach, these experiments have helped to elucidate the functional relevance of synapse-specific endocannabinoid transmission in the rewarding effects of ethanol.