Abstract:

Neuropsychiatric diseases, such as autism spectrum disorders (ASD) and schizophrenia, are severe and disabling disorders affecting millions of people worldwide. Accumulating evidence has implicated disturbances in GABAergic signaling in many psychiatric diseases, and it has been proposed that these diseases arise from an imbalance in neuronal excitation and inhibition (E/I). Recently, the cholecystokinin (CCK)-type inhibitory neuron in the hippocampus has been identified as a potential autism-related interneuron, as well as having an associated role in schizophrenia. Interestingly, CCK interneurons can release both a neuropeptide as well as neurotransmitter, often in opposing functional outcome. We aim to test a novel circuit-driven mechanism underlying the etiology of neuropsychiatric disease with the involvement of the CCK interneuron that releases both the inhibitory GABA transmitter and the often excitatory CCK neuropeptide. Building upon our preliminary data, we will utilize chemogenetic stimulation and in vitro and in vivo electrophysiology to dissect the how the excitatory action through CCK peptide and inhibitory action through GABA neurotransmission from the same neuron can modulate the E/I balance in the hippocampus. Furthermore, we will determine methods of manipulating this balance by using viral delivery of short hairpin RNAs to target selective aspects of CCK interneuron signaling and examining animals for circuit dysfunction and disease-related behavioral abnormalities. We believe that insights gained from this proposed study will leading to a better understanding of the causes of autism and schizophrenia, and may contribute to the development of effective therapeutic interventions for these devastating disorders.