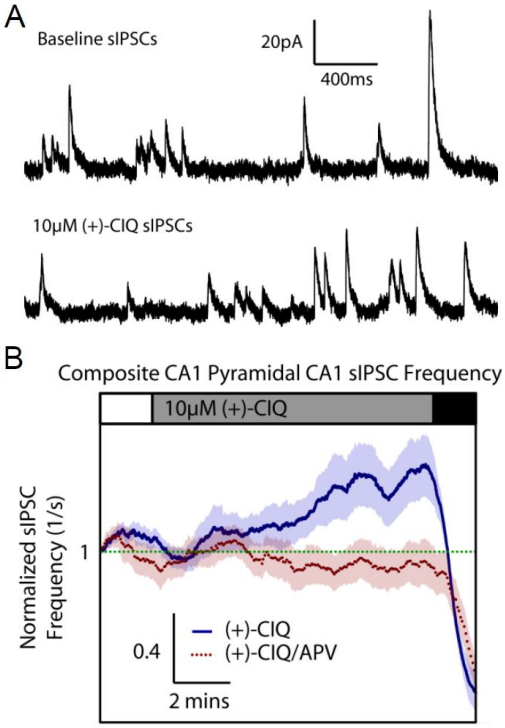
Novel Subunit-Selective Allosteric Modulators of NMDA Receptors

Glutamate receptors are ligand-gated channels that catalyze the transmembrane flux of cations in response to activation by the neurotransmitter glutamate. These receptors mediate fast and slow synaptic currents at almost all excitatory central synapses, and thus are critical for normal brain function and also implicated in a number of neurological diseases. The tetrameric receptors can be divided into three classes (AMPA, kainate, NMDA), each of which has multiple members creating heterogeneity in the CNS. At many synapses it still remains unclear which glutamate receptors mediate synaptic transmission. Given this lack of basic information about postsynaptic receptors and the role of this receptor family in neurological disease, there has been intense activity in the development of subunit-selective probes that can be used to obtain important information about synaptic receptor identity and function, and could also yield therapeutically-relevant insight into circuit regulation.

Among the glutamate receptors, NMDA receptors are tetrameric assemblies of two glycine-binding GluN1 subunits and two glutamate binding GluN2 subunits, of which four types exist (GluN2A,B,C,D). NMDA receptors mediate a slow Ca^{2+} permeable synaptic current when voltage dependent block by extracellular Mg^{2+} is relieved. The various GluN2 subunits show differential temporal and spatial distribution in the CNS, and thus provide an opportunity to develop region-specific modulators of NMDA receptor function based on compounds selective for one or another subunit. Despite the potential to develop compounds that can modulate NMDA receptors in specific brain structures afforded by the 4 GluN2 subunits, few advances in the development of subunit-selective antagonists have occurred between 1995-2010. To break this impasse rather than waiting for others to generate useful compounds, we developed and implemented a high-throughput screen designed to identify non-competitive inhibitors and potentiators of NMDA receptors that contained the GluN2C and GluN2D subunits in 2007-8. This screen was highly successful, and we identified over a dozen new classes of inhibitors or potentiators that prefer GluN2C and/or GluN2D subunits. We currently focus on both understanding the site and mechanism underlying regulation of NMDA receptors by both positive and negative allosteric modulators that we identified. We collaborate closely with Dr. Dennis Liotta in the Dept. Chemistry at Emory, a world renowned chemist with extensive experience (and success) with drug development. This medicinal chemistry campaign is advancing our understanding of multiple new classes of compounds. We also collaborate both with experts in molecular modeling and crystallography to determine the site of action for these compounds. We explore the effects of allosteric modulators at the level of the synapse, circuit, and whole animal, and use these new pharmacological tools to obtain to better understanding of normal brain functions such as learning and memory. Information gained with these tools about the role of NMDA receptors in excitatory synaptic transmission can provide insight into new therapeutic strategies to treat epilepsy, stroke, Parkinson's disease, schizophrenia, epilepsy, and depression



(+)-CIQ actions on spontaneous network activity. (A) sIPSC recordings from CA1 pyramidal cells before and during the application of the GLuN2C/D-selective positive allosteric modulator (+)-CIQ. (B) Composite rolling average of 30 sIPSC frequency from CA1 pyramidal cells in the presence of (+)-CIQ and (+)-CIQ/APV. A baseline sIPSC frequency was established (white box, aCSF/DMSO for (+)-CIQ recordings and aCSF/200 μM APV/DMSO for (+)-CIQ/APV recordings) followed by the addition of 10 μM (+)-CIQ (grey box). Experiments ended in 10 μM gabazine. The shaded area shows SEM. From Perszyk et al., 2016.