Novel subunit-selective allosteric modulators of NMDA receptor function

NMDA receptors are tetrameric assemblies of the glycine-binding GluN1 subunit and glutamate binding GluN2 subunits, of which four types exist (GluN2A,B,C,D). The various GluN2 subunits show differential temporal and spatial distribution in the CNS, and thus provide an opportunity to develop region-specific pharmacological regulation of NMDA receptor function based on compounds selective for one or another subunit. Despite the opportunity to develop compounds that can modulate NMDA receptors in specific brain structures, virtually no significant advances in the development of subunit-selective antagonists have occurred in over 15 years, with highly selective antagonists identified for only one GluN2 subunit (GluN2B). Similarly, no drug-like small molecule potentiators of NMDA receptors have been identified, despite long-standing hypotheses that such molecules might have utility in neurological disorders such as schizophrenia. To participate in breaking 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. This screen was highly successful, and to date we are working with over a dozen new and unique classes of inhibitors or potentiators that prefer some combination of GluN2C and/or GluN2D subunits. Some of these compounds appear highly selective, and medicinal chemistry performed in collaboration at Emory University has improved the potency of best-in-class compounds to sub-micromolar levels for multiple classes. We are currently studying all aspects of these new subunit-selective modulators—small molecule structure-function-relationship, site of action, mechanism of action, and effects in native receptors in isolated neurons, slices, and in vivo. We believe some of these new compounds will lead to development of highly selective research tools as well as the identification of new therapeutic strategies.