Allosteric modulation of glutamate receptors

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NMDA receptors (NMDARs) are ligand-gated ion channels that are tetrameric assemblies of 2 glycine-binding GluN1 subunits and 2 glutamate-binding GluN2 subunits. NMDARs respond to synaptically-released glutamate by producing a slow inward current mediated by Na^+ and Ca^{2+}. We hypothesize that 3 gating elements control opening of the pore, including 9 conserved residues (SYTANLAAF) that comprise the extracellular end of the M3 transmembrane helix, a short helix that is parallel to the plane of the membrane and precedes the M1 transmembrane helix, and a linker preceding the M4 transmembrane helix. We identified several allosteric modulators that act at the pre-M1 region, one of which reduces single channel conductance, an effect not previously observed for NMDAR modulators. For example, EU1622-14 reduces single channel conductance of NMDARs on cultured cortical neurons from 52, 44 pS in vehicle to 42, 35, and 28 pS (n= 7 outside out patches, Vm -80 mV). EU1622-14 also reduced the relative permeability of Ca^{2+} to Na^+ for recombinant GluN1/GluN2A and GluN1/GluN2B receptors by more than 2-fold ($p<0.05$, ANOVA). This is the first example of an exogenous drug-like allosteric modulator that can interact with the NMDAR to alter the relative permeability of ions, which has important biophysical implications. In addition, the precedent that Ca^{2+} permeability can be controlled pharmacologically creates a new potential therapeutic target with intriguing possibilities.