Role of NMDA receptors in the pathophysiology and treatment of status epilepticus

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SUMMARY

This review considers the role of N-methyl-d-aspartate receptors in the pathophysiology and treatment of status epilepticus (SE). NMDA receptors play a critical role in sustaining SE by mediating the plasticity of γ-aminobutyric acid (GABA)-A and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, neuronal loss, and epileptogenesis. In parallel, there is growing interest in using the NMDA receptor antagonist ketamine in the treatment of refractory SE. Ketamine has proved to be safe for use in refractory and super-refractory SE in patients. The pilot studies also suggest that ketamine may be efficacious for termination of refractory SE.

KEY WORDS: NMDA receptors, Ketamine, AMPA, GABA.

Structure and Pharmacology

N-methyl-d-aspartate (NMDA) receptors belong to the glutamate ionotropic receptor family. The molecular structure, biophysical properties, and integrative function of these receptors have been investigated extensively and were reviewed recently. Briefly, the receptor is sensitive to multiple inputs: the presence of the agonists glutamate or glycine, pH, and relief of acute voltage-dependent block by Mg$^{2+}$. The receptor is activated slowly and decays slowly; it allows prolonged entry of Ca$^{2+}$ into neurons. The NMDA receptor is composed of 4 subunits derived from 3 gene families: GluN1-3. Each receptor is a tetramer composed of 2 GluN1 subunits and either 2 GluN2 or 2 GluN3 subunits. Each subunit has an extracellular N-terminal domain, a transmembrane domain, and a C-terminal intracellular domain. Activation of NMDA receptors requires the presence of the agonist glutamate and the coactivator glycine or serine. There is evidence that GluN1 subunits predominantly bind ambient d-serine at synaptic and glycine at extrasynaptic sites. Cerebrospinal fluid (CSF) contains sufficient glycine and serine under basal conditions to saturate all glycine binding sites on the receptor. In addition to agonist binding, the receptor requires depolarization and removal of the magnesium block for the passage of Na$^+$ and Ca$^{2+}$ ions through the channel. This condition is ideal for activation during seizures, which entail prolonged sustained firing of neurons.

NMDA receptor function can be modulated by drugs acting at multiple sites. A large number of NMDA receptor modulators have been described. Multiple classes of
modulators are described: competitive antagonists at the agonist binding site, channel blockers, allosteric site inhibitors and agonists, and glycine site antagonists, among others. Several new subunit-specific receptor antagonists have been described. D(-)-2-Amino-5-phosphonopentanoic acid (APV) and analogs are competitive antagonists; ketamine, memantine, and MK-801 are noncompetitive antagonists; and ifenprodil is an allosteric inhibitor of NMDA receptors. The glycine binding site is modulated by endogenous polyamines. More recently, synthetic allosteric positive modulators of NMDA receptors have been identified. A comparison of the efficacy of NMDA receptor antagonists in terminating status epilepticus (SE) suggested that the noncompetitive antagonist MK-801 is superior to the competitive antagonist 3-(2-Carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP) and the pH site inhibitor ifenprodil in terminating experimental SE.

NMDA receptors are located in the postsynaptic membrane mixed with AMPA receptors or in extrasynaptic membranes. Synaptic receptors demonstrate slow activation and deactivation related to the biophysical properties of these receptors. Because these receptors require depolarization to remove the magnesium block, receptors located in the extrasynaptic membrane may be activated by glutamate diffused from synapses, especially during periods of increased activity and when the reuptake processes are compromised. Extrasynaptic NMDA receptors are trafficked between synapses and extrasynaptic membranes, and this is in part regulated by neuronal activity. GluN2A subunit is more likely to be present at synapses, whereas GluN2B is more commonly present at extrasynaptic sites. GluN2B subunit-containing receptor activation is associated with epilepsy development, and association with cell injury and death, and development of SE.

**ROLE OF NMDA RECEPTORS IN SE**

We consider 3 roles of NMDA receptors in the pathophysiology of SE. We then consider the potential use of ketamine in the treatment of SE in a clinical trial.

In several animal models of SE, NMDA receptor antagonists can terminate SE when used as a monotherapy, whereas they act synergistically with benzodiazepines in other models. In electrical stimulation models of SE, NMDA receptor antagonists can effectively terminate SE. In these models, NMDA antagonists are more effective in the prolonged, self-sustaining phase of SE. In electrical stimulation models, noncompetitive NMDA receptor antagonists are superior to competitive and allosteric modulators.

NMDA antagonists exert a synergistic action with benzodiazepines in terminating refractory SE. Benzodiazepines are extremely efficacious in terminating early SE; however, with the passage of time and as seizures continue, these drugs are less potent in terminating SE. A key challenge in SE research is to identify drugs that terminate benzodiazepine-refractory SE. In cholinergic stimulation models of SE, NMDA receptor antagonists alone are ineffective in terminating benzodiazepine-refractory SE. However, when these drugs are combined with benzodiazepines, they work synergistically to end seizures.

SE results in neuronal injury and death. Both necrotic and programmed cell death are reported to occur as a result of SE. It has long been known that NMDA receptors play an important role in the induction of cell loss during SE. Original studies on the excitotoxic effects of glutamate demonstrated that blocking NMDA receptors could block cell loss. NMDA receptor antagonists given during SE caused protection of CA1, CA3, the subiculum, the entorhinal cortex, and multiple other regions in the brain. Competitive NMDA receptor antagonists can also offer neuroprotection against SE-induced cell loss.

NMDA receptor–mediated excitatory synaptic currents and extrasynaptic receptor–mediated tonic currents are enhanced during SE in experimental animals. This was accompanied by accumulation of GluN1 on the postsynaptic membrane. There was increased colocalization of the GluN1 subunit with synaptic markers. Electron microscopic studies demonstrated movement of these subunits to the center of the synapse. Taken together, these studies suggested trafficking of the GluN1 subunit from the intracellular compartment to the cell membrane, which caused enhancement of synaptic and extrasynaptic NMDA receptor–mediated transmission.

NMDA receptors appear to play a key role in accelerating internalization of GABA_A receptors during SE. In the hippocampus, inhibitory postsynaptic currents in dentate granule cells and CA1 pyramidal neurons are diminished as SE proceeds. There is a reduction in the amplitude of synaptic currents, which suggests a diminished number of GABA_A receptors on the postsynaptic membrane. GABA_A receptors undergo constitutive endocytosis and exocytosis, which is modulated by neuronal activity.
is clathrin mediated through a binding site on the intracellular domain of GABA<sub>A</sub> receptor subunits. As seizures occur, the process of endocytosis is accelerated in a calcium-dependent manner. This accumulation of calcium in the cell is in part dependent on NMDA receptor activation during seizures.

Activation of NMDA receptors during SE also appears to play a role in the enhancement of AMPA receptor–mediated transmission. There is growing evidence that α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor–mediated transmission is enhanced during prolonged seizures. The amplitude of excitatory postsynaptic currents is increased, and they become rectifying in character. This change is associated with increased surface expression of the GluA1 subunit and diminished surface expression of the GluA2 subunit of AMPA receptors. It is proposed that this enhancement of AMPA receptor transmission is due to insertion of GluA1 subunits into postsynaptic membrane accompanied by accelerated endocytosis of GluA2 subunits of AMPA receptors. GluA1 subunit insertion into the cell membrane and enhancement of AMPA receptor–mediated transmission can be blocked by the NMDA receptor antagonists ketamine and MK-801.

NMDA receptor antagonists prevent delayed development of epilepsy in animal models. This protection against epileptogenesis has been demonstrated in the electrical stimulation model of SE, the lithium pilocarpine model, and others. This long-term protection is associated with prevention of downregulation of delta subunit–containing GABA<sub>A</sub> receptors and other effects. It has been proposed that NMDA receptor activation during SE leads to the activation of the ERK1/2 system, leading to downregulation of the delta subunit–containing GABA<sub>A</sub> receptors. Reduction in the delta subunit of GABA<sub>A</sub> receptors reduces the neurosteroid sensitivity of GABA<sub>A</sub> receptors in dentate granule cells of the hippocampus, which potentially compromises their gating function, thus rendering the whole hippocampus susceptible to seizures.

The role of NMDA receptors in neurotransmitter receptor plasticity during SE is displayed in Figure 1.

**Clinical Use of NMDA Receptor Antagonist in Treatment of SE**

Ketamine has been used increasingly to terminate refractory SE. It is a commonly used anesthetic that maintains blood pressure and respiratory drive. Ketamine has an elimination half-life of 4.9 h. In a single prospective study in patients, systolic and diastolic arterial pressure and heart rate remained unchanged in 9 patients treated with ketamine. Ketamine is a noncompetitive antagonist of NMDA receptors, in contrast to other third-line agents, such as propofol, midazolam, and pentobarbital, which act on GABA<sub>A</sub> receptors.

A recent review has summarized clinical experience with ketamine treatment of refractory SE. In the largest series of studies, 60 patients with refractory SE were treated with ketamine in institutions across North America. These uncontrolled observational studies suggest that ketamine can terminate refractory SE in 50–60% patients, whereas conventional third-line anesthetic agents such as midazolam or propofol have failed. There were no safety concerns raised in these studies. Furthermore, many patients could be weaned from vasopressors. Ketamine has been safely used for the treatment of refractory SE in children.

In light of strong evidence from experimental animals and a safety signal from clinical studies, it is time to design a definitive phase III clinical trial for the treatment of refractory SE with ketamine.

**DISCLOSURE**

I have no conflicts of interest to disclose. I confirm that I have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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