Revisiting NMDA receptor inhibitors that work differently hoping to treat brain injury and stroke

Over-activation of NMDA receptors, a subtype of glutamate receptors, has long been suspected to contribute to the development of the penumbral zone of damage that develops hours after a traumatic brain injury or stroke occurs. This area surrounds the infarct, dead tissue caused by impaired blood flow, and suffers from reduced glucose and oxygen supply, as well as reduced clearance of carbon dioxide and metabolites. These impairments prevent neurons from being able to maintain their normal functions causing aberrant release of the neurotransmitter glutamate and a reduced ability to clear glutamate results in a build-up of glutamate in extra-cellular spaces. A vicious cycle develops, leading to NMDA receptor activation by aberrant levels of glutamate, which causes harmful consequences to neuron health and leads to cell death. When neurons die they release internal stores of glutamate and other harmful factors that then spread outwardly beyond the affected tissue. The cycle starts again and increases the size of the penumbral zone. The volume of damaged tissue is often considered to be correlated with the patient's prognosis, and outcomes have been hypothesized to improve greatly if this cycle can be interrupted by molecules that inhibit NMDA receptor function. Representative NMDA receptor inhibitors progressed to clinical trials, which ultimately proved unsuccessful. Part of these failures has been attributed to poor trial design, patient variability, inherent complexity in determining improvements in patient outcome, as well as side-effects resulting from the molecules' actions on NMDA receptors in healthy brain regions. NMDA receptors also play a role in normal brain function, such that patients receiving treatment experienced disorientation and impaired cognition. To circumvent cognitive impairment, lower doses were administered, limiting the measureable beneficial effects. After these clinical trial failures, most pharmaceutical companies scaled back their neuroprotective programs involving NMDA receptors. Currently, there are still almost no effective treatments for traumatic brain injury and stroke, other than molecules which dissolve clots in a subset of patients to restore blood flow.

The goal of our study was to reduce the unwanted side-effects of NMDA receptor inhibitors and to spur efforts to find a therapeutic molecule for treating traumatic brain injury or stroke. Our laboratory identified a new class of NMDA receptor inhibitors via a high-throughput screen. Molecules in this class had promising properties, which led us to synthesize new analogues to use in experiments to understand how these molecules interact with and regulate NMDA receptors. We were able to identify the portions of the molecules where improvements could be made. Interestingly, we found that some of the new molecules partially inhibited NMDA receptors, even when used at saturating concentrations. This is different than previously known NMDA receptor inhibitors which cause complete inhibition, a likely cause for negative side-effects. This new property can be thought of as installing curtains on a window that reduce the intensity of incoming light instead of black-out shades, which block all light. We then tested the ability of the most potent molecule to block over-activation of NMDA receptors in neurons, mimicking what contributes to the development of the penumbral zone. We found that treatment with this molecule was neuroprotective and reduced the cell death as compared to control trials.

With the discovery of this series of molecules, we anticipate that interest will be renewed in the therapeutic use of NMDA receptor inhibitors in the treatment of traumatic brain injury and stroke. Future studies will be required to test if partial inhibition can avoid the side-effects which contributed to the earlier drug trial failures. If so, clinical trials could be conducted to determine whether molecules that partially inhibit NMDA receptors are capable of providing therapeutic benefit.

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