Selective strategy could lead to new approaches against schizophrenia

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A new class of compounds identified by researchers at Emory University School of Medicine could be developed into drugs for the treatment of schizophrenia. The compounds enhance signaling by molecules in the brain called NMDA receptors, which scientists believe are functioning at low levels in people with schizophrenia.

Led by Stephen Traynelis, PhD, professor of pharmacology, a team of Emory researchers sifted through thousands of chemicals and found one, called CIQ, which could selectively enhance the function of certain NMDA receptors without affecting others.

The results were published Oct. 5, 2010 by the journal *Nature Communications*.

The first author of the paper is Praseeda Mullasseril, PhD. The research was a collaboration with Dennis Liotta, PhD, professor of chemistry, and his colleagues.

Doctors now treat schizophrenia with a variety of antipsychotic drugs, but these can have several long-term side effects. The rationale for treating schizophrenia via NMDA receptors comes from the observation that when healthy people take the drugs ketamine or phencyclidine (PCP or angel dust), they temporarily experience the symptoms of schizophrenia, such as hallucinations, disorganized thoughts and flattened emotions.

"There is room for improvement in therapeutic treatment of schizophrenia," Traynelis says. "Exploration of alternative targets, such as the NMDA receptor, could potentially lead to expanded treatment options and improved outcomes for patients with schizophrenia."

Ketamine and phencyclidine both interfere with NMDA receptors. This has led scientists to the idea that pushing in the opposite direction chemically – enhancing rather than blocking NMDA receptors -- may help relieve schizophrenia's symptoms.

NMDA receptors act as gates that let electrical charges flow into neurons when enough of the neurotransmitter glutamate is present. They are essential for receiving signals in the brain connected with sensory perception, learning and memory.

NMDA receptors come in several forms. When assembled, they have two parts: one that stays the same throughout the brain, called NR1, and one that comes in four different varieties (NR2A, B, C and D) of varying prominence, depending on the region of the brain being examined.

Only a few known drugs can selectively target NMDA receptors comprised of different NR2 subunits. Traynelis' team was looking for chemicals that would only enhance function by the NR2C and NR2D forms. Previous studies have suggested that enhancement of these subunits may help people with schizophrenia.

"Enhancing NMDA receptor function might compensate for some of the deficits seen in patients with schizophrenia," he says. "Because NMDA receptors play a number of important roles in the brain, we sought to target only those subunits that have been suggested to potentially improve symptoms in patients with schizophrenia."

The team discovered a compound called CIQ that makes it easier for NMDA receptor gates to open, although it doesn't act alone; it still needs glutamate and glycine to bind to the NMDA receptor before CIQ can exert its actions. The scientists also discovered that the parts of the NR2C and NR2D NMDA receptors that are CIQ-sensitive are distinct from those regions of NMDA receptors known to interact with other known drugs.

"CIQ appears to act at a new, physically distinct site on the receptor that could offer an opportunity to manipulate receptor function in a variety of ways," Traynelis says.

"CIQ is not a drug or clinical candidate," he adds. "Rather, it marks the beginning of a process that involves fine tuning the structure to build potent, selective, and well-tolerated compounds. Later, these can be evaluated in clinical trials to determine whether the strategy of enhancing NMDA receptor signaling does indeed improve the lives of patients with schizophrenia. In addition, compounds emerging from this optimization process could become useful tools for dissecting NMDA receptor contributions to cognition, learning, memory, as well as other diseases."

More information: Mullasseril P, et al. A subunit-selective potentiator of NR2C- and NR2D-containing NMDA receptors. *Nat. Comm.* doi:10.1038/ncomms1085 (2010).

Provided by Emory University