Understanding schizophrenia: Researchers uncover new underlying mechanism

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(PhysOrg.com) -- A new way of thinking about the fundamental pathobiology of schizophrenia could one day lead to improved therapeutic approaches to treating this disorder. Researchers at the University of Toronto, the Hospital for Sick Children (SickKids) and Tufts University School of Medicine have linked proteins and genes that are implicated in schizophrenia in a novel way. The study is published in the March 27 advance online edition of *Nature Medicine*.

Schizophrenia is a disorder that affects one per cent of Canadians and 24 million people worldwide. A team of researchers led by Professor Michael Salter of physiology and a senior scientists at SickKids identified a biochemical pathway in the brain that may contribute to the neurobiological basis of schizophrenia.

"This is a paradigm shift in the way that we view the neural mechanisms of schizophrenia," said Salter. "With our discovery we have brought together in a new way pieces of the schizophrenia puzzle. We hope that the understanding we have put together will lead to new forms of treatment that are more effective than the ones that are currently available."

The scientists studied in mice two partner proteins, NRG1 and ErbB4, and the effect they have on a key brain receptor known as the N-methyl D-aspartate glutamate receptor (NMDAR). While NRG1 and ErbB4 have been genetically implicated in schizophrenia, the new study finds an unexpected link to NMDARs.

The NMDAR is a major component of synapses - the highly specialized sites of communication between the brain's billions of individual nerve cells - that is critical for many brain functions including learning and memory. Suppressed functioning of NMDARs was suspected in schizophrenia because drugs that block NMDARs cause the hallucinations and disordered thought that occur in schizophrenia.

It had been suspected that NRG1 and ErbB4 might suppress generally NMDAR function but the present study found this was not the case. Rather, the researchers discovered that NRG1 and ErbB4 work together through inhibiting another protein, Src. The link to NMDARs is that Src normally increases NMDAR function under circumstances when this is needed such as in learning and memory. The researchers found that by blocking Src, NRG1 and ErbB4 selectively prevented that critical boost in NMDAR function.

The researchers also studied the responses of nerve cells during brain activity that mimicked normal brain oscillations known as theta rhythm. Theta rhythm activity, which is critical for learning and memory, is impaired in individuals with schizophrenia. The researchers determined that by acting through Src, NRG1 and ErbB4 greatly reduced the nerve cell responses to theta rhythm activity.

The findings suggest new approaches to schizophrenia treatment by reversing the effects of NRG1 and ErbB4 through enhancing the Src boost of NMDARs. "The tricky part is that all of these proteins are involved in other functions of the body; we can't randomly enhance or inhibit them as this would lead to side effects," Salter said. "The key will be to develop clever ways to target the proteins in the context of the synapse."

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