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Researchers link two biological risk factors for schizophrenia

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(Medical Xpress) -- Johns Hopkins researchers say they have discovered a cause-and-effect relationship between two well-established biological risk factors for schizophrenia previously believed to be independent of one another.

The findings could eventually lead researchers to develop better drugs to treat the cognitive dysfunction associated with schizophrenia and possibly other mental illnesses.

Researchers have long studied the role played in the brain's neurons by the Disrupted-in-Schizophrenia 1 (DISC1) gene, a mutation with one of the strongest links to an increased risk of developing the debilitating psychiatric illness.

In a study published in the journal Molecular Psychiatry, the laboratory of Mikhail V. Pletnikov, M.D., Ph.D., in collaboration with the laboratory of Solomon H. Snyder, M.D., D.Sc., instead looked at the role the DISC1 gene plays in glia cells known as astrocytes, a kind of support cell in the brain that helps neurons communicate with one another.

"Abnormalities in glia cells could be as important as abnormalities in neuronal cells themselves," says Pletnikov, an associate professor of psychiatry and behavioral sciences at the Johns Hopkins University School of Medicine, and the study's leader. "Most gene work has been done with neurons. But we also need to understand a lot more about the role that genetic mutations in glia cells play because neuron-glia

interaction appears crucial in ensuring the brain operates normally."

Besides the paranoia and hallucinations that characterize the disease, schizophrenics have cognitive deficits, leaving them unable to think clearly or organize their thoughts and behavior.

Previous studies found that one of the roles of astrocytes is to secrete the neurotransmitter D-serine, which helps promote the transmission of glutamate in the brain, believed to be a key to cognitive function. Schizophrenics have decreased glutamate transmission. It appears, Pletnikov says, that people with DISC1 mutations associated with the psychiatric illness are faster to metabolize D-serine, which leads to a decrease in the apparently crucial transmitter.

In clinical trials, other researchers are trying to boost D-serine levels in people with schizophrenia to see if they can boost cognitive function.

In the new study, the Johns Hopkins researchers found that DISC1 is directly involved in regulating the production of D-serine by the enzyme known as serine racemase.

The researchers found that DISC1 normally binds to serine racemase and stabilizes it. The mutant DISC1 in patients with schizophrenia cannot bind with serine racemase, and instead destabilizes and destroys it. The result is a deficiency of D-serine.

The Hopkins researchers bred mice with the mutant DISC1 protein expressed only in astrocytes and, as predicted, the animals had decreased levels of D-serine. These mice also showed abnormal behavior "consistent with schizophrenia," Pletnikov says. For example, the rodents showed sensitivity to psycho-stimulants that target glutamate transmission. By treating the mice with D-serine, the scientists were able to ameliorate the schizophrenic-like symptoms. Mice without the DISC1

mutation in astrocytes had normal D-serine levels.

Pletnikov says that in the future, researchers hope that they can target the unstable junction between the abnormal DISC1 and serine racemase. If drugs, for example, can be found to increase glutamate transmission in humans, doctors may be able to improve cognitive function in schizophrenics. He says a DISC1 mutation may also be an important risk factor in other psychiatric disorders.

"Abnormal glutamate transmission is believed to be present in patients with bipolar disorder, major depression and possibly anxiety disorders, so our findings could apply to other psychiatric diseases," he says.

Provided by Johns Hopkins University School of Medicine

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