Taming suspect gene reverses schizophrenia-like abnormalities in mice

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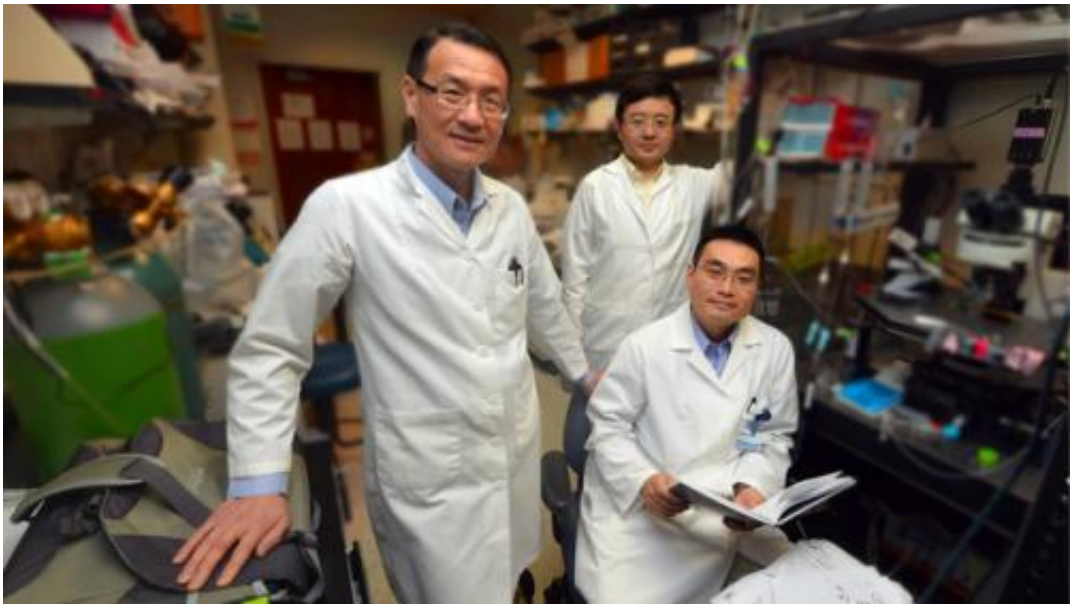

This image show, from left: Lin Mei, M.D., Ph.D., Dong-Min Yin, Ph.D. and Yong-Jun Chen, Ph.D., Medical College of Georgia. Credit: Medical College of Georgia

Scientists have reversed behavioral and brain abnormalities in adult mice that resemble some features of schizophrenia by restoring normal expression to a suspect gene that is over-expressed in humans with the illness. Targeting expression of the gene Neuregulin1, which makes a protein important for brain development, may hold promise for treating at least some patients with the brain disorder, say researchers funded by the National Institutes of Health.

Like patients with schizophrenia, adult mice biogenetically-engineered to have higher Neuregulin 1 levels showed reduced activity of the brain messenger chemicals glutamate and GABA. The mice also showed behaviors related to aspects of the human illness. For example, they interacted less with other animals and faltered on thinking tasks.

"The deficits reversed when we normalized Neuregulin 1 expression in animals that had been symptomatic, suggesting that damage which occurred during development is recoverable in adulthood," explained Lin Mei, M.D., Ph.D., of the Medical College of Georgia at Georgia Regents University, a grantee of NIH's National Institute of Mental Health (NIMH).

Mei, Dong-Min Yin, Ph.D., Yong-Jun Chen, Ph.D., and colleagues report on their findings May 22, 2013 in the journal *Neuron*.

"While mouse models can't really do full justice to a complex brain disorder that impairs our most uniquely human characteristics, this study demonstrates the potential of dissecting the workings of intermediate components of disorders in animals to discover underlying mechanisms and new treatment targets," said NIMH Director Thomas R. Insel, M.D. "Hopeful news about how an illness process that originates early in development might be reversible in adulthood illustrates the promise of such translational research."

Schizophrenia is thought to stem from early damage to the developing fetal brain, traceable to a complex mix of genetic and environmental causes. Although genes identified to date account for only a small fraction of cases, evidence has implicated variation in the Neuregulin 1 gene. For example, postmortem studies have found that it is overexpressed in the brain's thinking hub, or prefrontal cortex, of some people who had schizophrenia. It codes for a chemical messenger that plays a pivotal role in communication between brain cells, as well as in

brain development.

Prior to the new study, it was unclear whether damage caused by abnormal prenatal Neuregulin 1 expression might be reversible in adulthood. Nor was it known whether any resulting behavioral and brain deficits must be sustained by continued errant Neuregulin 1 expression in adulthood.

To find out, the researchers engineered laboratory mice to mimic some components of the human illness by over-expressing the Neuregulin 1 gene in the forebrain, comparable to the prefrontal cortex in humans. Increasing Neuregulin 1 expression in adult animals was sufficient to produce behavioral features, such as hyperactivity, social and cognitive impairments, and to hobble neural communications via the messenger chemicals glutamate and GABA.

Unexpectedly, the abnormalities disappeared when the researchers experimentally switched off Neuregulin 1 overexpression in the adult animals. Treatment with clozapine, an antipsychotic medication, also reversed the behavioral abnormalities. The researchers traced the glutamate impairment to an errant enzyme called LIMK1, triggered by the overexpressed Neuregulin 1 – a previously unknown potential pathological mechanism in schizophrenia.

The study results suggest that even if their illness stems from disruptions early in brain development, adult patients whose schizophrenia is rooted in faulty Neuregulin 1 activity might experience a reduction in some of the symptoms following treatments that target overexpression of the protein, say the researchers.

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