Experimental cancer drug reverses schizophrenia in adolescent mice

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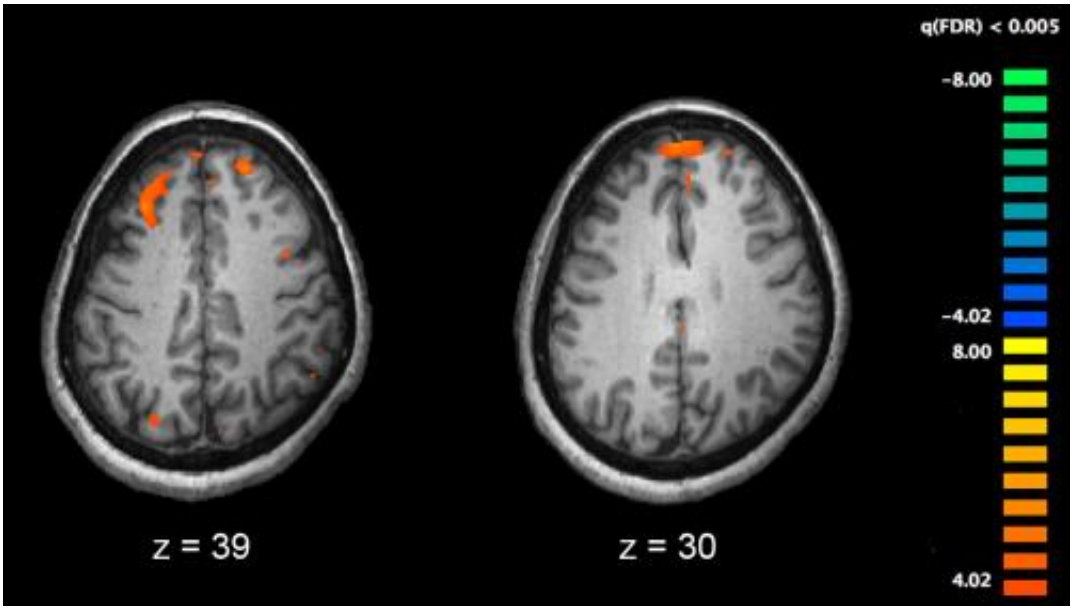

Functional magnetic resonance imaging (fMRI) and other brain imaging technologies allow for the study of differences in brain activity in people diagnosed with schizophrenia. The image shows two levels of the brain, with areas that were more active in healthy controls than in schizophrenia patients shown in orange, during an fMRI study of working memory. Credit: Kim J, Matthews NL, Park S./PLoS One.

Johns Hopkins researchers say that an experimental anticancer compound appears to have reversed behaviors associated with schizophrenia and restored some lost brain cell function in adolescent mice with a rodent version of the devastating mental illness.

The drug is one of a class of compounds known as PAK inhibitors, which have been shown in animal experiments to confer some protection from brain damage due to Fragile X syndrome, an inherited disease in humans marked by mental retardation. There also is some evidence, experts say, suggesting PAK inhibitors could be used to treat Alzheimer's disease. And because the PAK protein itself can initiate cancer and cell growth, PAK inhibitors have also been tested for cancer.

In the new Johns Hopkins-led study, reported online March 31 in the *Proceedings of the National Academy of Sciences*, the researchers found that the compound, called FRAX486, appears to halt an out-of-control biological "pruning" process in the schizophrenic brain during which important neural connections are unnecessarily destroyed.

Working with mice that mimic the pathological progression of schizophrenia and related disorders, the researchers were able to partially restore disabled neurons so they could connect to other nerve cells.

The Johns Hopkins team says the findings in teenage mice are an especially promising step in efforts to develop better therapies for schizophrenia in humans, because schizophrenia symptoms typically appear in late adolescence and early adulthood.

"By using this compound to block excess pruning in adolescent mice, we also normalized the behavior deficit," says study leader Akira Sawa, M.D., Ph.D., a professor of psychiatry and behavioral sciences at the Johns Hopkins University School of Medicine. "That we could intervene in adolescence and still make a difference in restoring brain function in these mice is intriguing."

For the mouse experiments, Sawa and his colleagues chemically turned down the expression of a gene known as Disrupted-in-Schizophrenia 1

(DISC1), whose protein appears to regulate the fate of neurons in the cerebral cortex responsible for "higher-order" functions, like information processing.

In studies of rodent brain cells, the researchers found that a DISC1 deficit caused deterioration of vital parts of the neuron called spines, which help neurons communicate with one another.

Reduced amounts of DISC1 protein also impact the development of a protein called Kalirin-7 (KAL7), which is needed to regulate another protein called Rac1. Without enough DISC1, KAL7 can't adequately control Rac1 production and the development of neuronal spines. Excess Rac1 apparently erases spines and leads to excess PAK in the mice.

By using FRAX486 to reduce the activity of PAK, the researchers were able to protect against the deterioration of the spines caused by too little DISC1, halting the process. This normalized the excess pruning and resulted in the restoration of missing spines. They were able to see this by peering into the brains of the mice with DISC1 mutations on the 35th and 60th day of their lives, the equivalent of adolescence and young adulthood.

Sawa, who is also director of the Johns Hopkins Schizophrenia Center, cautions that it has not yet been shown that PAK is elevated in the brains of people with schizophrenia. Thus, he says, it is important to validate these results by determining whether this haywire PAK cascade is also occurring in humans.

In the mice, the researchers also found that their behavior improved when PAK inhibitors were used. The mice were tested for their reaction to noises. There is a neuropsychiatric phenomenon in which any organism will react less to a strong, startling sound when they have first been primed by hearing a weaker one. In schizophrenia, the first noise

makes no impact on the reaction to the second one.

The mice in the study showed improvements in their reactions after being treated with the PAK inhibitor. The drug was given in small doses and appeared to be safe for the animals.

"Drugs aimed at treating a disease should be able to reverse an already existing defect as well as block future damage," Sawa says. "This compound has the potential to do both."

More information: PAK inhibitors rescue DISC1-deficit-triggered dendritic spine deterioration: novel therapeutic potential for schizophrenia, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1321109111

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