Brain tumor disorder impairs chemical system responsible for attention

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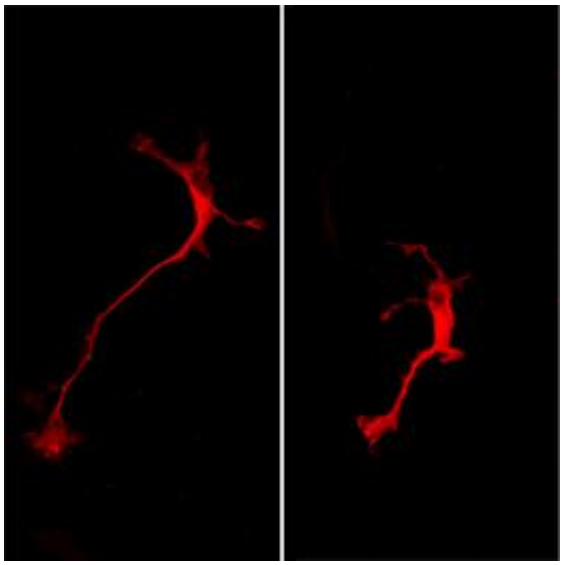

Scientists have discovered that mutations in the neurofibromatosis 1 (NF1) gene impair the development of branches of the neurons in the brain that generate dopamine, possibly causing attention deficits. On the left is a dopaminergic neuron from a normal mouse; on the right is the same type of neuron taken from a mouse with a mutated NF1 gene. Image: DAVID GUTMANN

(PhysOrg.com) -- A genetic condition that increases risk of brain tumors may also impair development of the brain system that facilitates attention, according to researchers at Washington University School of Medicine in St. Louis.

The findings, observed in a mouse model, help explain the attention deficits and learning disabilities sometimes seen in children with neurofibromatosis 1 (NF1), an inherited disorder that increases risk of brain tumor formation. And they suggest drugs already approved by the FDA may be especially effective for treating learning and behavior problem in children with NF1.

"Not only were we able to show that our mouse model of NF1 has attention deficits similar to patients, we also were able to treat them and restore attention to normal levels with Ritalin," says David H. Gutmann, MD, PhD, the Donald O. Schnuck Family Professor of Neurology.

The findings are published online in the journal *Human Molecular Genetics*.

Gutmann is director of the Washington University Neurofibromatosis Center, a national referral center for patients with all forms of neurofibromatosis. The center is active in clinical trials and basic research to help develop innovative new approaches for treating patients with NF, which affects more than 100,000 people in the United States. Gutmann is also co-director of the neuro-oncology program at the Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine.

Gutmann collaborated with David Wozniak, PhD, research professor of psychiatry, to evaluate a NF1 mouse model developed at Washington University for problems with learning and attention. They found that the mice were less likely to pay attention to new objects in their environment or to explore their surroundings. When they treated the mice with Ritalin, the mice gave their surroundings normal levels of attention.

"We know that Ritalin blocks nerve cells from recycling a neurotransmitter called dopamine, so next we looked at dopamine levels in the brains of these mice," Gutmann says.

Jacquelyn Brown, PhD, postdoctoral research associate in Gutmann's laboratory, showed that the NF1 mutant mice had low levels of dopamine in particular brain areas and that treatment with Ritalin restored these levels to near normal. She also learned that brain cells in the dopaminergic system, which generate dopamine, had shorter branches, leading to fewer synapses or connections where the cells interact. This likely leads the cells to

release less dopamine, according to the researchers.

Gutmann and his colleagues recently received a U.S. Department of Defense grant to further study learning and behavior in NF1 mutant mice. They plan to use the funds to better understand the cognitive decline that affects some NF1 patients years after treatment. These declines occur in a significant number of NF1 patients and may strike 10-12 years after treatment, typically in the middle to late teenage years.

"We'll be looking at the mouse model to see if it suffers a similar decline months after treatment," he says. "If we can better understand the causes of these declines, future treatments for brain tumors may involve not only chemotherapy, but also neuroprotective strategies to reduce the collateral damage to nerve cells in the developing brains of children."

More information: Brown JA, Emnett RJ, White CR, Yuede C, Conyers S, O'Malley KL, Wozniak DF, Gutmann DH. Reduced striatal dopamine underlies the attention system dysfunction in neurofibromatosis-1 mutant mice. Human Molecular Genetics, online September 2010.

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