Brain scans reveal drugs' effects on attention

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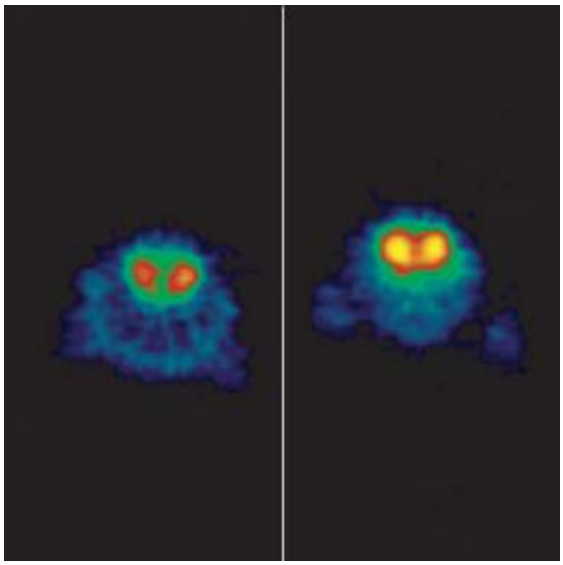

Scientists have developed a way to use PET scans to test if drugs are helping mice that have been genetically engineered to have a form of attention deficit. In the brain of the altered mouse (right), low dopamine levels result in a brighter image. (DAVID GUTMANN, MD, PHD)

(Medical Xpress) -- Scientists have developed a way to evaluate new treatments for some forms of attention deficit disorder.

Working in mice, researchers at Washington University School of Medicine in St. Louis showed that they can use brain scans to quickly test whether drugs increase levels of a brain chemical known as dopamine.

In a study published last year, the same group found that raising dopamine levels in mice alleviates attention deficits caused by neurofibromatosis type 1 (NF1), a condition that affects more than 100,000 people in the United States. Approximately 60 percent to 80 percent of children with NF1 have some type of attention deficit problem.

"Many kids with NF1 really struggle in school, and finding ways to help alleviate attention problems is a high priority," says David H. Gutmann, MD, PhD, the Donald O. Schnuck Family Professor of Neurology. "The technique we've refined may make it possible to match specific treatments to the patients with NF1 and attention deficit who are most likely to benefit from those treatments."

The results appear online in *Experimental Neurology*.

Symptoms of NF1-related attention deficits are similar to those that affect children in the general population. But it's unclear whether the brain changes that underlie these problems in children with NF1 are similar to the brain changes that cause attention deficits in the general population.

"This mouse model may not be a perfect model for all forms of attention deficit, but it is a terrific model for one type of attention system dysfunction," Gutmann says. "Greater understanding of what goes wrong in some children with NF1 could lead to new insights into a broader variety of attention problems."

Gutmann is director of the Washington University Neurofibromatosis (NF) Center, a national referral center for patients with all forms of neurofibromatosis. The center is active in basic science research and clinical trials, with the goal of developing innovative new approaches for treating patients with NF.

Gutmann and his colleagues have developed genetically engineered mice that develop NF1-related attention problems and brain tumors.

Last year, Gutmann showed that one of these lines of mice had lower levels of dopamine in part of the brain. Following treatment with the drug Ritalin, both the brain dopamine levels and the attention deficits in these mice were restored to normal.

"Prior to our study, there was no molecular basis for using Ritalin to treat children with NF1 and attention deficits, so its use depended on the pediatrician's practice, the severity of the attention deficit and how comfortable the parents were with the use of medication," Gutmann says. "In general, only the most severely affected kids are being treated, but that may change in the future."

For the new study, Gutmann collaborated with Robert Mach, PhD, professor of radiology, who had been working with an imaging agent, raclopride, that binds to dopamine receptors in the brain. Raclopride can be detected by positron emission tomography (PET) scans.

When Jinbin Xu, PhD, research instructor in radiology, used raclopride to test dopamine levels in untreated mice, lower levels of brain dopamine allowed for greater raclopride binding, creating a brighter PET image. Following Ritalin treatment, the raclopride binding decreased.

"This finding suggested that raclopride PET imaging could be used as a platform for preclinical testing of drugs that may affect brain dopamine levels," Gutmann says. "We can get an image in an hour and assess the effects of the drug on mouse behavior in a day."

Washington University scientists including David Wozniak, PhD, and Kelly Diggs-Andrews, PhD, and former Washington University researcher Jackie Brown, PhD, used the new method to test additional drugs. A compound designed to block the recycling of dopamine was successful in restoring dopamine levels. In contrast, another drug, currently in a clinical trial for learning problems in children with NF1, did not boost dopamine levels or correct the attention deficits.

Conducting similar tests in children using current PET technology involves significant radiation exposure, Gutmann says. However, a new scanner now available at Washington University that combines PET and MRI will lower the radiation exposure, making it possible to consider this method for children with NF1.

"At some point, we envision a prescreening process that identifies children with reduced dopamine levels most likely to respond to Ritalin or other medications," Gutmann says. "As we learn more about the different ways attention deficits arise in these children, it may be possible to use the prescreening data and preclinical drug tests in mouse models to select the best drug for each patient."

More information: Brown JA, Xu J, Diggs-Andrews KA, Wozniak DF, Mach RH, Gutmann DH. PET imaging for attention deficit preclinical drug testing in neurofibromatosis-1 mice. *Experimental Neurology*, online.

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