Intestinal protein may have role in ADHD, other neurological disorders

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A biochemical pathway long associated with diarrhea and intestinal function may provide a new therapeutic target for treating ADHD (Attention Deficit Hyperactivity Disorder) other neuropsychiatric disorders, according to a team of scientists from China and the United States reporting Aug. 11 in *Science*.

Scientists have for the last quarter century studied the intestinal membrane receptor protein, guanylyl cyclase-C (GC-C) for its role in diarrheal disease and other intestinal functions, according to Mitchell Cohen, M.D., U.S. author on the study and director of Gastroenterology, Hepatology and Nutrition at Cincinnati Children's Hospital Medical Center. In fact, it had been thought that GC-C was found primarily in the intestine.

In the current study, scientists in China who collaborated with Dr. Cohen discovered that the receptor is also expressed in critical areas of the brain. The senior author on the study is Dr. Minmin Luo, a researcher at the National Institute of Biological Sciences and Tsinghua University in Beijing.

Using a mouse model developed in Dr. Ralph Giannella's laboratory at the University of Cincinnati, in which the GC-C receptor is deleted, or knocked out, the researchers found the mice exhibit hyperactivity and attention deficits. It is the first time that GC-C has been linked to neuropsychiatric disorder, according to the researchers.

"We show that the neurons selectively express GC-C and that its activation amplifies the excitatory responses mediated by other receptors on dopamine neurons in the midbrain," said Dr. Luo. "Working through a protein kinase called PKG, GC-C activity increases brain dopamine levels and thus regulate mouse attention and activity level."

When the researchers treated the GC-C knockout mice with amphetamine-based ADHD medication and a PKG activator, it reversed their hyperactive, inattentive behavior.

"The results indicate important behavioral and physiological functions for the GC-C/PKG signaling pathway in the brain," said Dr. Luo. "The data also suggest new therapeutic targets for neuropsychiatric disorders related to malfunctions of midbrain dopamine receptors."

One of the most prevalent human behavioral disorders, ADHD has been linked to imbalances in the dopamine system. The researchers noted in the study that its findings - mice exhibiting reduced dopamine levels and related behavioral problems - are consistent with the biochemical characteristics of human ADHD.

"This could make the GC-C knockout mouse a good research model for ADHD and other behavioral disorders," said Dr. Cohen. "Efforts to develop activators or inhibitors of the GC-C/PKG signaling pathway may lead to novel treatments for other disorders, such schizophrenia, Parkinson's disease and addiction."

Provided by Cincinnati Children's Hospital Medical Center