

How schizophrenia develops: Major clues discovered

October 16 2007

Schizophrenia may occur, in part, because of a problem in an intermittent on/off switch for a gene involved in making a key chemical messenger in the brain, scientists have found in a study of human brain tissue. The researchers found that the gene is turned on at increasingly high rates during normal development of the prefrontal cortex, the part of the brain involved in higher functions like thinking and decisionmaking – but that this normal increase may not occur in people with schizophrenia.

The study was funded by the National Institutes of Health's National Institute of Mental Health (NIMH) and National Institute of Child Health and Human Development.

The gene, GAD1, makes an enzyme essential for production of the chemical messenger, called GABA. The more the gene is turned on, the more GABA synthesis can occur, under normal circumstances. GABA helps regulate the flow of electrical traffic that enables brain cells to communicate with each other. It is among the major neurotransmitters in the brain.

Abnormalities in brain development and in GABA synthesis are known to play a role in schizophrenia, but the underlying molecular mechanisms are unknown. In this study, scientists discovered that defects in specific epigenetic actions – biochemical reactions that regulate gene activity, such as turning genes on and off so that they can make substances like the GAD1 enzyme – are involved.



Results of the research were published in the October 17 issue of the *Journal of Neuroscience*, by Schahram Akbarian, MD, PhD, Hsien-Sung Huang, PhD student, and colleagues at the University of Massachusetts Medical School and Baylor College of Medicine.

"This discovery opens a new area for exploration of schizophrenia," said NIMH Director Thomas R. Insel, MD. "Studies have yielded very strong evidence that schizophrenia involves a decrease in the enzymes, like GAD1, that help make the neurotransmitter GABA. Now we're starting to identify the mechanisms involved, and our discoveries are pointing to potential new targets for medications."

Another enzyme, Mll1, may play a role in the epigenetic actions. For genes to be turned on, temporary structural changes in certain proteins - histones - must take place to expose the genes' blueprints in DNA. The researchers found evidence that, in schizophrenia, changes in Mll1 activity may interfere with this process in histones whose alterations enable the GAD1 blueprint to be exposed.

The researchers also showed, in mice, that antipsychotic medications like clozapine appear to correct this epigenetic flaw. This raises the possibility of developing new medications aimed at correcting defects in the mechanisms involved.

Finding more precise molecular targets for development of new schizophrenia medications is a key effort, because it can lead to more effective treatments with fewer side effects. Clozapine and other current antipsychotic medications are effective for many patients, but not all, and they can cause side effects severe enough that some people choose to stop treatment.

The researchers also found that people with three different variations of the GAD1 gene – variations previously associated with schizophrenia –



also were more likely to have indicators of a malfunction in brain development. Among them were indicators of altered epigenetic actions related to GABA synthesis.

"We've known that schizophrenia is a developmental disease, and that something happens in the maturation of the prefrontal cortex during this vulnerable period of life. Now we're beginning to find out what it is, and that sets the stage for better ways of preventing and treating it," Akbarian said.

Source: National Institute of Mental Health

Citation: How schizophrenia develops: Major clues discovered (2007, October 16) retrieved 8 May 2024 from <u>https://medicalxpress.com/news/2007-10-schizophrenia-major-clues.html</u>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.