New target explored for psychiatric drug development

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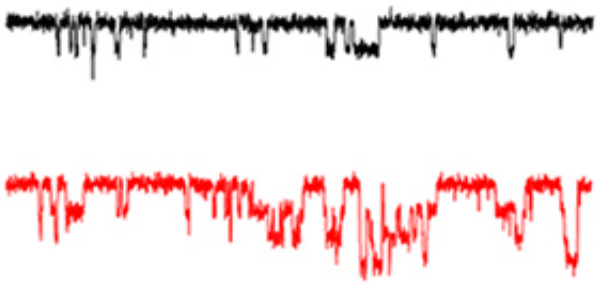

Researchers have discovered that a molecule known as an oxysterol can stimulate receptors on brain cells key to cognitive function. The finding may aid development of new types of antipsychotic drugs. The black (top) line shows an untreated receptor. The red line, with significantly more downward peaks, shows oxysterol is activating the receptor. Credit: Zorumski Laboratory

(Medical Xpress)—In a surprising discovery, neuroscientists have found that a breakdown product of cholesterol in the brain may be a target for developing new drugs to treat schizophrenia and other mental illnesses.

Although the research is in its early stages, the finding comes at a crucial time. Most existing drugs to treat schizophrenia work in similar ways,

targeting dopamine receptors in the brain, but many patients don't respond well to the medications or can't tolerate the side effects.

The investigators, from Washington University School of Medicine in St. Louis, SAGE Therapeutics and Weill Cornell Medical College, report in The *Journal of Neuroscience* that a molecule known as an oxysterol helps control a different type receptor in the brain that is key in cognitive function.

Because the naturally occurring oxysterol molecule interacts with receptors not normally associated with medications used to treat serious psychiatric illnesses, the researchers believe it could be useful in the development of new types of antipsychotic drugs.

The molecule, called 24(S)-hydroxycholesterol, targets NMDA receptors in the brain, which are important in processes thought to be the biological underpinnings of learning and memory.

Although most existing antipsychotic drugs instead target dopamine receptors, drugs that block NMDA receptor function—such as the anesthetic ketamine and the street drug PCP—can produce psychotic symptoms or relieve depression, depending on the dosage. The researchers believe that molecules that enhance activity in NMDA receptors may help control psychotic symptoms and limit the learning and memory problems that accompany illnesses such as schizophrenia.

"One of the big problems for patients with schizophrenia is that they have difficulty with working memory and learning new things," said principal investigator Charles F. Zorumski, MD. "The cognitive problems are one reason the illness is so disabling, and this oxysterol appears to provide us with a target to treat those difficulties."

Zorumski, the Samuel B. Guze Professor of Psychiatry and

Neurobiology and head of the Department of Psychiatry, also directs Washington University's Taylor Family Institute for Innovative Psychiatric Research. The institute is conducting research to find how oxysterols and related neurosteroids work in the brain. Both occur naturally and are key in the functioning of brain networks for cognition, emotion and motivation.

"Cholesterol doesn't travel from the body into the brain, so the brain has to make its own to manufacture neural membranes and white matter, and oxysterols play a key role in that," Zorumski said. "Both neurosteroids and oxysterols are derivatives of cholesterol."

Current evidence suggests the production of these molecules in the brain is affected by stress and by psychiatric disorders such as depression and schizophrenia. The Taylor Family Institute scientists believe that enhancing the activity of oxysterols or neurosteroids may help the brain function more normally.

In the new study, researchers measured responses to a tiny electrical stimulus in brain cells taken from the hippocampus of rats and mice. They also conducted experiments that record the electrical activity in individual brain cells. Zorumski and his colleagues found that when neurons were exposed to the oxysterol 24(S)-hydroxycholesterol, the function of their NMDA receptors was enhanced, suggesting that the molecule may be useful in stimulating the activity of those receptors.

The research team also identified a pair of synthetic derivatives of 24(S)-hydroxycholesterol that exert similar effects on NMDA receptors in brain cells. Those derivatives, called SGE-201 and SGE-301, were able to reverse impairments in cognitive and social behavior produced by PCP-like drugs in mice and rats.

Studies of natural and synthetic oxysterols are ongoing at SAGE

Therapeutics, a Massachusetts-based pharmaceutical company that recently licensed technology based on research conducted by scientists at the Taylor Family Institute. That license dealt with compounds designed to modulate a different type of brain receptor, called a GABA receptor, again with the idea of creating more effective treatments for psychiatric diseases. The goal of the collaboration is to more quickly move discoveries made in the lab into clinical trials to find more effective treatments for psychiatric illnesses.

The paper's first author, Steven M. Paul, MD, chairs SAGE's Scientific Advisory Board. He also directs the Helen and Robert Appel Alzheimer's Disease Research Institute and is a professor of neuroscience, psychiatry and pharmacology at Weill Cornell Medical College.

At Washington University, Zorumski and his colleagues plan to begin analyzing oxysterol levels in the brains of people with schizophrenia.

"There's an opportunity to quickly move from our observations about 24(S)-hydroxycholesterol to actually measuring oxysterol levels in the cerebrospinal fluid of individuals with schizophrenia," he said. "We don't really know whether levels of this oxysterol are altered in people with schizophrenia, but we'd like to find out."

Provided by Washington University School of Medicine in St. Louis