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Schizophrenia linked to dysfunction in molecular brain pathway activated by marijuana

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Alterations in a molecular brain pathway activated by marijuana may contribute to the cognitive symptoms of schizophrenia, according to a report in the July issue of *Archives of General Psychiatry*, one of the JAMA/Archives journals.

Expression of the cannabinoid 1 receptor (CB1R), the site of action of the main chemical ingredient of marijuana, is significantly reduced in the brains of individuals with schizophrenia. Activation of CB1R impairs signaling by gamma-aminobutyric acid (GABA), an important neurotransmitter essential for core cognitive processes such as working memory. The use of marijuana in individuals with schizophrenia appears to worsen this deficit in GABA synthesis.

Since reduced GABA is known to be present in schizophrenia, these findings suggest possible new drug targets that could help to improve function in people with the mental illness, University of Pittsburgh School of Medicine researchers report.

"Heavy marijuana use, particularly in adolescence, appears to be associated with an increased risk for the later development of schizophrenia, and the course of illness is worse for people with schizophrenia who use marijuana," said David A. Lewis, M.D., corresponding author of the study and UPMC Endowed Professor in Translational Neuroscience, Western Psychiatric Institute and Clinic,

University of Pittsburgh School of Medicine.

"We wanted to understand the biological mechanisms that could explain these observations, and with this study, I believe that we can narrow down at least part of the 'why' to CB1R, the receptor for both tetrahydrocannabinol (THC), the main psychoactive ingredient in marijuana, and the brains own cannabinoid chemical messengers."

Dr. Lewis and his colleagues examined specimens of brain tissue collected after death from 23 people with schizophrenia and 23 normal comparison subjects matched for a number of factors, including age and sex. The researchers evaluated levels of CB1R messenger RNA and protein, and also measured levels of glutamic acid decarboxylase (GAD-67), an enzyme that makes GABA, and cholecystokinin (CCK), a neuropeptide released from GABA neurons that, among other actions, regulates the production of the brain's own cannabinoids.

"CB1R levels were significantly 15 percent lower in the subjects with schizophrenia," Dr. Lewis said. "We measured these biochemical messengers using three techniques, and each time got the same answer – less CB1R in people with schizophrenia." This reduction, he noted, appears to be the brain's way of compensating for lower levels of GABA, and the use of marijuana defeats this compensation.

"These findings may provide insight into the biological basis of why cannabis use worsens schizophrenia, and, as a result, identify a novel target for new drug development that could improve treatments available for schizophrenia," said Dr. Lewis.

Source: University of Pittsburgh