GABA deficits disturb endocannabinoid system

January 24 2012

Changes in the endocannabinoid system may have important implications for psychiatric and addiction disorders. This brain system is responsible for making substances that have effects on brain function which resemble those of cannabis products, e.g., marijuana.

The endocannabinoid system is of particular interest in the field of schizophrenia research because exposure to cannabis products during adolescence and young adulthood appears to increase the risk for developing schizophrenia. Also, in studies examining brain tissue collected from people who had schizophrenia, changes in the endocannabinoid system were highly correlated with changes in the principal inhibitory chemical messenger system in the brain, the gamma-aminobutyric acid (GABA) system.

The current study was conducted in order to research the relationship between changes in the GABA system and changes in the endocannabinoid system. Led by Dr. David Lewis at the University of Pittsburgh, researchers made genetic manipulations in mice that selectively reduced the GABA system function by decreasing the expression of the enzyme that makes GABA, GAD67, or by decreasing the expression of the principal receptor target for endocannabinoids in the brain, the cannabinoid 1 receptor (CB1R), in order to determine whether a change in one is sufficient to cause a change in the other.

Using these techniques, the researchers demonstrated that reduced expression of GAD67 can lead to reduced expression of CB1R, but not

vice versa.

"Because activation of the CB1R suppresses GABA release, lower levels of CB1R may help augment GABA release from nerve terminals that have below normal amounts due to reduced GABA synthesis," said Dr. Lewis of the results. "This evidence suggests that reduced GABA signaling is an 'upstream' event in the disease process of schizophrenia and that lower CB1R is a compensation to help normalize GABA signaling."

These findings indicate that GABA abnormalities in schizophrenia are what trigger the disturbances in the endocannabinoid system. Importantly, cannabis use also alters GABA activity in the brain.

"While the whole story is still developing, from these data, it looks like developmental deficits in GABA systems are sufficient to disturb the function of the endocannabinoid system. This could be an important clue to the link between cannabis use and psychosis," commented Dr. John Krystal, editor of *Biological Psychiatry*.

Additional research will be necessary to further explore such links, including investigations into whether and/or how cannabis exposure affects the relationship between GAD67 and CB1R.

More information: The article is "Cortical Glutamic Acid Decarboxylase 67 Deficiency Results in Lower Cannabinoid 1 Receptor Messenger RNA Expression: Implications for Schizophrenia" by Stephen M. Eggan, Matthew S. Lazarus, Samuel R. Stoyak, David W. Volk, Jill R. Glausier, Z. Josh Huang, and David A. Lewis (doi: 10.1016/j.biopsych.2011.09.014). The article appears in *Biological Psychiatry*, Volume 71, Issue 2 (January 15, 2012)