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# Link between depression and inflammatory response found in mice

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Vanderbilt University researchers may have found a clue to the blues that can come with the flu – depression may be triggered by the same mechanisms that enable the immune system to respond to infection.

In a study in the December issue of *Neuropsychopharmacology,* Chong-Bin Zhu, M.D., Ph.D., Randy Blakely, Ph.D., William Hewlett, M.D., Ph.D., and colleagues activated the immune system in mice to produce "despair-like" behavior that has similarities to depression in humans.

"Many people exhibit signs of lethargy and depressed mood during flu-like illnesses," said Blakely, director of the Vanderbilt Center for Molecular Neuroscience. "Generally these have been treated as just a consequence of being physically ill, but we think there is likely to be something more brain-centric at work here."

Blakely and his colleagues previously reported that inflammatory cytokines can enhance the activity of the serotonin transporter (SERT), which regulates the supply of the neurotransmitter serotonin in the synapse, or gap between nerve cells.

Elevations in SERT activity remove serotonin from brain synapses at an enhanced rate and, based on studies in animal models and man, would be predicted to increase the risk for mood and anxiety disorders. Indeed, a class of antidepressant drugs called selective serotonin reuptake inhibitors (SSRIs) – Prozac, Zoloft, etc. – work by blocking the ability of SERT to eliminate serotonin.

In the current study in mice, the researchers triggered pro-inflammatory cytokine production. Within 30 to 60 minutes, SERT was activated in the brain and the animals displayed despair-like behavior.

Remarkably, this behavior was not observed when cytokine production was triggered in mice lacking the SERT gene. Similarly, a drug that blocks inflammatory molecule signaling also prevented stimulation of SERT and the despair behavior. "It's as if these inflammatory molecules are an 'anti-Prozac,'" Blakely said.

In their paper, the researchers cautioned that "we do not presume that changes in SERT activity alone are sufficient to induce the full spectrum of depression traits, nor that our animal model can reproduce all the elements of a complex neuropsychiatric disorder."

"Nonetheless, we were able to identify a mechanism that may be a engaged, even without inflammation, to impact risk for depressive illness," Blakely said.

More study is needed. Identifying genetic variations in the SERT activation pathway, for example, might suggest additional sources of genetic risk for depression. "Our work suggests that novel therapies targeting inflammation-linked pathways may be of use in the treatment of mood disorders," he said.

Zhu is research associate professor of Pharmacology, Blakely is the Alan D. Bass Professor of Pharmacology and professor of Psychiatry, and Hewlett is associate professor of Psychiatry and Pharmacology.

Provided by Vanderbilt University Medical Center