Team identifies a molecular switch linking infectious disease and depression

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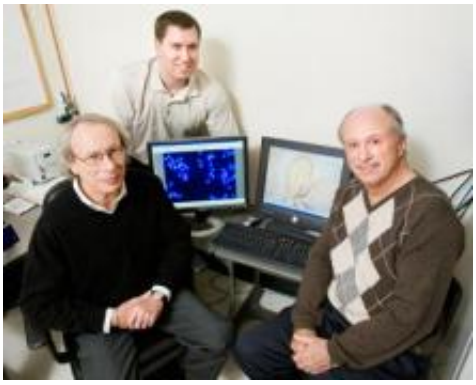

Animal sciences professors Robert Dantzer, Jason O'Connor and Keith Kelley (left to right) found that IDO is essential to the process by which chronic inflammation induces depression. Credit: Photo by L. Brian Stauffer, U. of I. News Bureau.

Researchers at the University of Illinois report that IDO, an enzyme found throughout the body and long suspected of playing a role in depression, is in fact essential to the onset of depressive symptoms sparked by chronic inflammation.

Their study, just published online in the Journal of Immunology, is the first to identify IDO (indoleamine 2,3 dioxygenase) as a molecular switch that induces depressive symptoms in some cases of chronic inflammation.

Doctors have known for decades that patients with chronic inflammation, such as that linked to coronary heart disease or rheumatoid arthritis, are more likely than others to become depressed. Some pro-inflammatory drugs, such as interferon-alpha, which is used to treat Hepatitis C and a cancer known as malignant melanoma, also induce symptoms of depression in a significant number of patients.

In the new study, mice were exposed to Bacille Calmette-Guérin (BCG), a vaccine used in many parts of the world to prevent tuberculosis. BCG produces low-grade, chronic inflammation in mice, which can be detected by measuring levels of certain immune system proteins, called inflammatory cytokines, in the blood and brain.

Mice exposed to BCG display the normal symptoms of illness (lack of appetite, reduced activity), but after these symptoms fade the mice continue to exhibit depressive-like behaviors that can be reversed with antidepressants, said animal sciences and pathology professors Keith Kelley and Robert Dantzer, who led the study.

Even after they recover from their sickness, the BCG-infected mice are much more passive than non-infected mice when in an inescapable situation. When placed in a bucket of water for a few minutes, for example, they struggle less to escape and spend more time floating passively, the researchers report.

"The mice that we're calling depressed give up more quickly. While physically able, the mice quit trying to escape," said animal sciences professor Jason O'Connor, first author on the study.

"But if you give them anti-depressants, the depressive-like behavior goes away," Kelley said.
"So the next question is, how can this be?" Dantzer said. "What is the biological molecular switch which makes them go from sickness to

depression?"

The researchers knew that infection causes immune cells to produce cytokines, signaling proteins that help the body fight infection. These proteins also activate IDO in the body and brain. IDO degrades the amino acid tryptophan, producing metabolites that affect animal and human behavior. Previous studies have found a strong correlation between an increase in these metabolites and the depressive symptoms seen in some patients.

An analysis of gene regulation in the mouse brains showed that exposure to BCG increased expression of IDO and two cytokines known to induce IDO: tumor necrosis
factor-alpha and interferon-gamma.

Because IDO degrades tryptophan, which is the precursor of serotonin, a brain chemical known to positively influence mood, scientists have hypothesized that the depression seen in patients with inflammatory disease was due to a decrease in serotonin in the brain. But a check of serotonin in the brains of mice with depressive-like behavior showed otherwise, Dantzer said.

"The brain is able to compensate for the decrease in tryptophan," he said.

To test whether IDO was essential to the depressive-like behaviors seen in mice, the researchers gave mice a drug that inhibits IDO and ran the experiment again. Just as before, the mice exposed to BCG exhibited typical sickness behavior (low appetite, reduced activity), from which they soon recovered. But pretreatment with the IDO inhibitor eliminated the subsequent development of depressive-like behavior. Mice that had the IDO gene deleted were also completely resistant to the depressive-like behavior seen in normal mice exposed to BCG.

"This is the first study to directly implicate IDO in depression related to chronic inflammation," Kelley said.

The researchers suspect that the metabolites produced when IDO degrades tryptophan are in some way promoting depression. More research will establish if that is true, they said.

In the meantime, the study highlights IDO as a potential target for development of new antidepressant drugs.

The study also demonstrates the robust link between the immune system and the nervous system, a connection often ignored by immunologists and neurologists, Kelley said.

To reduce this barrier between the two fields of study, Kelley and Dantzer launched the Integrative Immunology and Behavior program at Illinois. It supports interdisciplinary research on how inflammatory processes in the immune system and brain influence behavior and mental health.

"For years, no one considered that an infection somewhere in the body could affect the brain," Kelley said. "But as (University of Texas immunologist) Ed Blalock said in 1984, the immune system is a sensory organ. The immune system is exquisitely adapted as a sensory system to 'see' infectious agents. And it communicates that information to the brain."

Source: University of Illinois at Urbana-Champaign (news : web)

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