MedicalXpress

Mouse research links adolescent stress and severe adult mental illness

January 17 2013

Working with mice, Johns Hopkins researchers have established a link between elevated levels of a stress hormone in adolescence—a critical time for brain development—and genetic changes that, in young adulthood, cause severe mental illness in those predisposed to it.

The findings, reported in the journal *Science*, could have wide-reaching implications in both the prevention and treatment of schizophrenia, severe depression and other mental illnesses.

"We have discovered a mechanism for how environmental factors, such as stress hormones, can affect the brain's physiology and bring about mental illness," says study leader Akira Sawa, M.D., Ph.D., a professor of psychiatry and behavioral sciences at the Johns Hopkins University School of Medicine. "We've shown in mice that stress in adolescence can affect the expression of a gene that codes for a key neurotransmitter related to mental function and psychiatric illness. While many genes are believed to be involved in the development of mental illness, my gut feeling is environmental factors are critically important to the process."

Sawa, director of the Johns Hopkins Schizophrenia Center, and his team set out to simulate social isolation associated with the difficult years of adolescents in human teens. They found that isolating healthy mice from other mice for three weeks during the equivalent of rodent adolescence had no effect on their behavior. But, when mice known to have a genetic predisposition to characteristics of mental illness were similarly isolated, they exhibited behaviors associated with mental illness, such as

hyperactivity. They also failed to swim when put in a pool, an indirect correlate of human depression. When the isolated mice with genetic risk factors for mental illness were returned to group housing with other mice, they continued to exhibit these abnormal behaviors, a finding that suggests the effects of isolation lasted into the equivalent of adulthood.

"Genetic risk factors in these experiments were necessary, but not sufficient, to cause behaviors associated with mental illness in mice," Sawa says. "Only the addition of the external stressor—in this case, excess cortisol related to social isolation—was enough to bring about dramatic behavior changes."

The investigators not only found that the "mentally ill" mice had elevated levels of cortisol, known as the stress hormone because it's secreted in higher levels during the body's fight-or-flight response. They also found that these mice had significantly lower levels of the neurotransmitter dopamine in a specific region of the brain involved in higher brain function, such as emotional control and cognition. Changes in dopamine in the brains of patients with schizophrenia, depression and mood disorders have been suggested in clinical studies, but the mechanism for the clinical impact remains elusive.

To determine whether cortisol levels were influencing dopamine levels in the brain and adult behavioral patterns in the abnormal mice, the investigators gave them a compound called RU486, known to block cells from receiving cortisol. (The drug is commonly known as the "abortion pill.") All symptoms subsided. RU486 has also been studied in a clinical trial of people with difficult-to-treat psychotic depression, showing some benefits. "The mice swam longer, they were less hyper and their dopamine levels normalized," Sawa says.

To shed light on how and why the mice got better, Sawa and his team studied the gene tyrosine hydroxylase (Th) and found an epigenetic

change, essentially the addition of a methyl group to one of the gene's DNA letters, limiting the gene's ability to do its job, which is to create an enzyme that regulates dopamine levels. Without a fully functioning Th, dopamine levels are abnormally low.

Scientists have long studied gene mutations, permanent DNA changes that can tweak the normal function of a particular gene. But epigenetic alterations do not change the actual letters of the DNA sequence. Instead, they add a chemical group like methyl that can affect the function of the DNA. These changes can be transient, whereas genetic mutations are permanent.

Sawa says the new study points to the need to think about better preventive care in teenagers who have mental illness in their families, including efforts to protect them from social stressors, such as neglect. Meanwhile, by understanding the cascade of events that occurs when cortisol levels are elevated, researchers may be able to develop new compounds to target tough-to-treat psychiatric disorders with fewer side effects than RU486 has.

Provided by Johns Hopkins University School of Medicine