Anorexia-like condition in mice triggered by combination of genetic risk, stress, dieting

11 April 2016

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In a new study, researchers from Columbia University Medical Center (CUMC) described a new mouse model featuring a combination of genetic and environmental risk factors that can trigger the compulsive restriction of food intake seen in patients with anorexia nervosa. The findings may help to identify new prevention and treatment strategies for the eating disorder in humans.

The study was published online in the journal *Translational Psychiatry*.

Researchers have long suspected that a combination of genetic, biological, psychological, and sociocultural variables raise the risk of anorexia. While previous models of anorexia included some of these variables, none were able to capture the elements of social stress and genetic susceptibility to anxiety and anorexia that appear to contribute to the onset of the disorder in humans, particularly in adolescents.

"We think that for the first time, we have a mouse model of anorexia that closely resembles the conditions leading up to the disease in humans," said study leader Lori Zeltser, PhD, associate professor of pathology & cell biology and a researcher in the Naomi Berrie Diabetes Center. "And this model not only shows us the most important factors that contribute to the onset of anorexia, it's also helping us to identify signaling pathways in the brain that ultimately drive this potentially fatal eating disorder."

Anorexia is the third most common chronic illness among adolescents in the US, with a lifetime prevalence ranging from 0.3 to 0.9 percent in females and 0.1 to 0.3 percent in males. The disorder has a mortality rate of 8 to 15 percent, the highest of any psychiatric disease. There is no cure for anorexia.

For the new mouse model, the researchers exposed adolescent mice with at least one copy of a variant of the BDNF gene, which has been associated with anorexia and anxiety in mice and humans, to social stress and caloric restriction.

"One driver of anorexia in humans is peer pressure, specifically, the desire to be thin," said Dr. Zeltser. "People assumed that you couldn't replicate that in a mouse. We decided to take peer pressure out of the equation and focus on social stress, which can be accomplished by housing mice alone, instead of in groups."

The mice were then placed on a calorie-restricted diet, which usually precedes the development of anorexia in adolescent humans and may act as a trigger for eating disorders. In the study, the impact of dieting was simulated by reducing the mice's caloric intake by 20 to 30 percent—roughly equivalent to the caloric reduction of a typical human dieter.

"In the end, we've achieved a model that closely replicates the factors that elicit anorexic behavior in

humans," said lead author Moneek Madra, PhD, a lecturer in the Institute of Human Nutrition at CUMC.

The researchers found that adolescent mice with the gene variant, when exposed to both social isolation stress and caloric restriction, were much more likely than controls to avoid eating. Changes in feeding behavior did not occur when the environmental variables were imposed during adulthood. When the researchers subjected adolescent mice with the gene mutation to either social stress or caloric restriction, but not both, the animals exhibited little change in feeding behavior.

"Our findings show that having the at-risk genotype alone is not sufficient to cause anorexia-like behavior, but it confers susceptibility to social stress and dieting, especially during adolescence," said Dr. Zeltser. "You need all of these variables in place to see this robust effect on eating behavior."

The CUMC team is currently using the new mouse model to study signaling pathways in the brain that drive anorexic behavior, with the ultimate goal of identifying therapeutic targets.

The study is titled, "BDNF-Val66Met variant and adolescent stress interact to promote susceptibility to anorexic behavior in mice."

Provided by Columbia University Medical Center