Low levels of brain chemical may lead to obesity

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A brain chemical that plays a role in long term memory also appears to be involved in regulating how much people eat and their likelihood of becoming obese, according to a National Institutes of Health study of a rare genetic condition.

Brain derived neurotrophic factor (BDNF) is, as its name implies, produced in the brain. Studies of laboratory animals have suggested it also helps control appetite and weight. The NIH study, appearing in the August 28 *New England Journal of Medicine*, provides the first strong evidence that BDNF is important for body weight in human beings as well.

The NIH researchers studied children and adults with WAGR syndrome, a rare genetic condition. The researchers found that some of the people with this syndrome lack a gene for BDNF and have correspondingly low blood levels of the substance. The people in this subgroup also have unusually large appetites and a strong tendency towards obesity.

"This is a promising new lead in the search for biological pathways that contribute to obesity," said Duane Alexander, M.D., director of the NIH's Eunice Kennedy Shriver National Institute of Child Health and Human Development. "This finding may eventually lead to the development of new drugs to regulate appetite in people who have not had success with other treatments."

The study's first author was Joan C. Han, M.D. and the senior author was

Jack A. Yanovski, M.D., Ph.D., both of NICHD's Unit on Growth and Obesity. Other authors of the study were from the National Human Genome Research Institute and the National Institute on Drug Abuse, also part of the NIH. Funding for the study was provided by the NICHD and the NIH Office of Rare Diseases.

WAGR syndrome is an acronym for the complex of symptoms seen in people who have the condition. These include Wilms tumor, a tumor of the kidneys; aniridia, absence of the iris, in the eye; genital and urinary tract abnormalities; and mental retardation. WAGR syndrome occurs in one out of every 500,000 to 1 million persons.

People with WAGR syndrome lack genes that are grouped on chromosome 11. All people with WAGR syndrome lack two specific genes, called WT1 and PAX6, but each person can also be missing other nearby genes. For the most part, human chromosomes are arranged in pairs, and the genetic deletions found in WAGR syndrome occur on only one of the two copies of chromosome 11.

WT1 and PAX6 are located in the region of the chromosome that's near the gene for BDNF. For this reason, the NIH researchers examined chromosome 11 from WAGR syndrome patients to learn if the gene for BDNF was affected, explained Dr. Yanovski.

Studies of mice had determined that animals missing a working copy of the BDNF gene were prone to excessive eating and obesity. Studies in human beings, however, hadn't proved that BDNF was important in people.

In the current study, the NIH researchers conducted analyses of chromosome 11 in 33 patients with WAGR syndrome. A total of 19 patients (58 percent) had deletions of all or a major proportion of one copy of the gene for BDNF. By age 10, all of the 19 were obese and

were reported to have a strong tendency to overeat. Moreover, all of the 19 had blood levels of BDNF that were roughly 50 percent lower than those of patients who had two working copies of the BDNF gene. The patients who had two working copies of the BDNF gene were no more likely to develop childhood onset obesity than the general population, and did not report unusually high levels of overeating.

Dr. Yanovski explained that BDNF is believed to work in combination with a variety of other substances that regulate appetite and body weight. Chief among these is leptin, a hormone found to be involved in signaling hunger. Dr. Yanovski added that release of BDNF in the hypothalamus, a part of the brain involved in controlling eating, is believed to be indirectly triggered by leptin. Studies of the relationship between the two, and of BDNF's action on tissues, may lead to the development of new drugs to treat obesity in some individuals.

Source: NIH/National Institute of Child Health and Human Development