Overeating and obesity triggered by lack of BDNF

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According to the Centers for Disease Control and Prevention, close to one-third of the population in the United States is obese and another third is overweight. Excessive weight gain is elicited by alterations in energy balance, the finely modulated equilibrium between caloric intake and expenditure. But what are the factors that determine how much food is consumed?

Part of the mystery is unfolding in the laboratory of Maribel Rios, PhD, at the Sackler School of Graduate Biomedical Sciences at Tufts University School of Medicine in Boston. Through their work, Rios and colleagues have demonstrated for the first time that a protein called brain-derived neurotrophic factor (BDNF) is critical in mediating satiety in adult mice. Their findings are published in the December 26 issue of *The Journal of Neuroscience*.

Mice in which the Bdnf gene was deleted in two of the primary appetite-regulating regions of the brain ate more and became significantly heavier than their counterparts. “Prior to this study, we knew that the global lack of BDNF and/or its receptor during development leads to overeating and obesity in young mice.

However, it remained unclear and controversial whether BDNF mediated satiety in adult animals. Our recent findings demonstrate that BDNF synthesis in the ventromedial (VMH) and dorsomedial hypothalamus (DMH) is required for normal energy balance. Additionally, because the mice examined in this study were genetically

altered in adulthood, we were able to establish that BDNF acts as a satiety signal in the mature brain independently from its putative actions during development of the brain.

This important distinction might help define disease mechanisms and critical periods of intervention for the treatment and prevention of obesity disorders," says Rios, corresponding author and an assistant professor of neuroscience at the Sackler School.

The obesity exhibited by BDNF-depleted mice appears to arise solely from overconsumption of calories. "Normal body weight was restored in mutant mice when food access was limited to that of normal mice, indicating that deletion of the Bdnf gene in the VMH and DMH does not affect the expenditure side of the energy balance equation," adds Rios.

In a series of related experiments, the researchers used advanced molecular and surgical techniques to measure levels of BDNF mRNA, a precursor of active BDNF protein, in relation to nutritional status. Thaddeus Unger, a graduate student at the Sackler School and the study's first author, describes the results of these analyses.

"The amount of BDNF mRNA produced decreased during periods of fasting. However, when the mice were exposed to glucose, a macronutrient," Unger notes, "we observed a rapid, but transient, increase in the expression of BDNF and its receptor. These changes occurred specifically in the VMH, which is known to be involved in the regulation of food intake." The researchers confirmed that glucose acts directly in the brain, rather than through peripheral pathways, to increase BDNF expression. "Direct administration of BDNF into the brain," states Rios, "also led to an immediate increase in the levels of an early-response gene and marker of nerve-cell activation in both the VMH and the DMH. These results suggest that BDNF is a fast-acting signal inducing neuronal activity within neural circuits involved in appetite

control."

"Mice with site-specific perturbation of BDNF expression did not exhibit behavioral abnormalities typically observed in mice with global deletion of the Bdnf gene throughout the brain, such as hyperaggression, depressive-like behavior, and hyperactivity," notes Rios. "The absence of these behaviors suggests that BDNF expression in the VMH and DMH is not required for regulation of non-appetite-related behaviors."

"Our results establish that BDNF plays a prominent and direct role in the regulation of energy balance in adult mice." states Rios. "It appears that this signaling pathway acts, at least partly, through short-term mechanisms and that BDNF synthesis in the VMH and DMH is required for suppression of appetite."

While she notes that additional studies are needed to further pinpoint the cellular and molecular targets of BDNF action, Rios says, "This work brings us closer to elucidating the brain pathways that rely on BDNF to modulate food intake." She adds that "the relevance of the BDNF signaling pathway in human disease is highlighted by the obesity exhibited by certain humans carrying mutations or abnormalities in the genes coding for BDNF or its receptor. This is bound to be an important area of obesity research as more than a quarter on the American population has been estimated to carry mutations in the Bdnf gene."

Source: Tufts University