Neuroscience study uncovers new player in obesity

January 7 2014

This is an image of a weight scale. Credit: CDC/Debora Cartagena

A new neuroscience study sheds light on the biological underpinnings of obesity. The in vivo study, published in the January 8 issue of the *Journal of Neuroscience*, reveals how a protein in the brain helps regulate food intake and body weight. The findings reveal a potential new avenue for the treatment of obesity and may help explain why medications that are prescribed for epilepsy and other conditions that interfere with this

protein, such as gabapentin and pregabalin, can cause weight gain.

The protein – alpha2/delta-1 – has not been linked previously to obesity. A team led by Maribel Rios, Ph.D., associate professor in the department of neuroscience at Tufts University School of Medicine, discovered that alpha2/delta-1 facilitates the function of another protein called brain-derived neurotrophic factor (BDNF). A previous study by Rios determined that BDNF plays a critical role in appetite suppression, while the current study identifies a central mechanism mediating the inhibitory effects of BDNF on overeating.

"We know that low levels of the BDNF protein in the brain lead to overeating and dramatic obesity in mice. Deficiencies in BDNF have also been linked to obesity in humans. Now, we have discovered that the alpha2/delta-1 protein is necessary for normal BDNF function, giving us a potential new target for novel obesity treatments," said Rios, also a member of the cellular and molecular physiology and neuroscience program faculties at the Sackler School of Graduate Biomedical Sciences at Tufts.

Rios and colleagues discovered that low levels of BDNF were associated with decreased function of alpha2/delta-1 in the hypothalamus, a brain region that is critical to the regulation of food intake and weight. When the team inhibited the alpha2/delta-1 protein in normal mice, mice ate significantly more food and gained weight. Conversely, when the team corrected the alpha 2/delta-1 deficiency in mice with reduced BDNF levels, overeating and weight gain were mitigated. In addition, blood sugar levels (related to diabetes in humans) were normalized.

"We blocked activity of the alpha2/delta-1 protein in mice using gabapentin. These mice ate 39 percent more food, and as a consequence gained substantially more weight than control mice over a seven-day period," said first author Joshua Cordeira, Ph.D., a graduate of the

neuroscience program at the Sackler School and member of Rios's lab. This study is related to his Ph.D. thesis.

"When we re-introduced alpha2/delta-1 in obese mice lacking BDNF in the brain, we saw a 15-20 percent reduction in food intake and a significant reduction in weight gain. Importantly, metabolic disturbances associated with obesity, including hyperglycemia and deficient glucose metabolism, were greatly reduced by restoring the function of alpha2/delta-1," added Rios.

Some individuals who take gabapentin and pregabalin report weight gain. Both gabapentin and pregabalin are anticonvulsants, also used to treat nerve pain from, for example, shingles or diabetes. The findings from the Rios lab suggest that these drugs might contribute to weight gain by interfering with alpha2/delta-1 in the hypothalamus. This new understanding of alpha2/delta-1's role in appetite may allow researchers to develop complementary treatments that can prevent weight gain for patients taking these medications.

"We now know that alpha2/delta-1 plays a critical role in healthy BDNF function. The finding improves our understanding of the intricate neuroscience involved in appetite control. The next phase of our research will be to unravel the mechanisms mediating the satiety effects of alpha2/delta-1 in the hypothalamus," said Rios.

This latest finding builds on Rios's previous studies of BDNF and its role in regulating body weight. Earlier work by Rios established BDNF as an essential component of the neural circuits governing body weight in adult mice. Rios also determined that BDNF expression in two regions of the brain is required to suppress appetite.

More information: Cordeira JW, Felsted JA, Teillon S, Daftary S, Panessiti M, Wirth J, Sena-Esteves M, Rios M. The *Journal of*

Neuroscience. "Hypothalamic dysfunction of the thrombospondin receptor α2δ-1 underlies the overeating and obesity triggered by BDNF deficiency." Published January 8, 2014 DOI: 10.1523/JNEUROSCI.1572-13.2014