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Hormone combination effective and safe for treating obesity in mice

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Scientists at Indiana University and international collaborators have found a way to link two hormones into a single molecule, producing a more effective therapy with fewer side effects for potential use as treatment for obesity and related medical conditions.

The studies were carried out in the laboratories of Richard DiMarchi, the Standiford H. Cox Distinguished Professor of Chemistry and the Linda & Jack Gill Chair in Biomolecular Sciences in the IU Bloomington College of Arts and Sciences, and of Matthias Tschöp, professor of medicine and director of the Institute of Diabetes and Obesity, Helmholtz Center Munich, Germany. Results were published online this week by the journal *Nature Medicine*.

Researchers combined a peptide hormone from the digestive system, GLP-1, with the hormone estrogen and administered it to obese laboratory mice. While both GLP-1 and estrogen have demonstrated efficacy as therapy for obesity and adult-onset diabetes, the combination was more effective in producing weight loss and other beneficial results than using either compound on its own. And it produced fewer adverse effects, such as excessive tissue growth linked to tumor formation.

"We find that combining the hormones as a single molecule dramatically enhanced their efficacy and their safety," DiMarchi said. "The combination improves the ability to lower body weight and the ability to manage glucose, and it does so without showing the hallmark toxicities associated with estrogen."

The researchers believe GLP-1 acts as a "medicinal chaperone," targeting estrogen to the hypothalamus and pancreas, which are involved with metabolic processes. The precise targeting reduces the likelihood that the estrogen will produce negative effects, such as cancer and stroke.

Brian Finan, a former doctoral student in DiMarchi's lab, is the lead author of the paper, "Targeted estrogen delivery reverses the metabolic syndrome."

Co-authors include Bin Yang and Vasily Gelfanov, research scientists in the IU Bloomington Department of Chemistry, and DiMarchi. Finan is now a post-doctoral researcher at the Helmholtz Zentrum München in Germany, directed by Tschöp, who is DiMarchi's longtime collaborator and a corresponding co-author. Affiliations of the other 20 co-authors include the University of Cincinnati where, also led by Tschöp, many of the in vivo pharmacology and molecular mechanism studies were conducted; Northwestern University; and research laboratories in Germany and China.

Associated with what health authorities are calling a global epidemic of obesity, the metabolic syndrome consists of obesity associated with other factors such as high blood pressure, high triglycerides, hyperglycemia and low HDL cholesterol. The International Diabetes Federation estimates that as much as 20 percent of the world's adult population has some form of the metabolic syndrome and that they are three times as likely to have a heart attack or stroke and five times as likely to develop adult-onset diabetes as people without the syndrome.

DiMarchi said investigation continues in the optimization of the peptide-based hormone conjugates with an emphasis on determining the specific mechanism of biological action and identification of an optimal drug candidate suitable for human study. The combination of other peptides

and nuclear hormones for targeting other medical conditions holds considerable promise and opportunity for future research.

Provided by Indiana University