Understanding the role of glucose-dependent insulinotropic polypeptide in managing diabetes and obesity

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Scientists led by Dr. Timo Müller from Helmholtz Munich and the German Center for Diabetes Research (DZD) have now discovered that

glucose-dependent insulinotropic polypeptide (GIP) decreases body weight by interacting with specific inhibitory neurons in the brain. These new findings are published in *Nature Metabolism*.

Obesity and type 2 diabetes are two closely interconnected health challenges that are on the rise globally. Recent breakthroughs in the treatment were pioneered by Helmholtz Munich scientists and led to the development of so-called GIPR:GLP-1R co-agonists. These are compounds designed to target two specific hormone receptors in the human body: glucose-dependent insulinotropic polypeptide receptor (GIPR) and glucagon-like peptide-1 receptor (GLP-1R).

The receptors are involved in regulating glucose metabolism and insulin secretion and their pharmacological targeting promotes weight loss and reduction in food intake. However, the exact mechanisms and specific neuronal populations through which GIP affects energy balance and food intake remained so far largely elusive.

GIP induces weight loss through inhibitory neurons in the brain

Dr. Timo Müller and his team shed light on the underlying molecular mechanisms and the role of GIP. In their new study, the researchers demonstrate that GIP acts in the brainstem via specific inhibitory neurons. In detail, the GIPR:GLP-1R co-agonist reduces body weight and food intake through GIPR signaling in inhibitory neurons in the brain, the so-called GABAergic neurons. If the GIPR is absent in these GABAergic neurons, the weight-reducing effects of GIP vanish.

"For the first time, these data illustrate that GIP regulates body weight and food intake in the brain by stimulating GABAergic neurons and emphasizes the necessity of the GIPR on these neurons for this ability to

decrease body weight and food intake," says Timo Müller, senior author of the paper.

"Our data offer valuable insights into the mechanisms of GIPR:GLP-1R co-agonists, which can now be used to specifically target the brain GIP system for next generation anti-obesity drugs," adds Arek Liskiewicz, first author of the study.

More information: Liskiewicz et al, Glucose-dependent insulinotropic polypeptide (GIP) regulates body weight and food intake via GABAergic neurons in mice. *Nature Metabolism* (2023). DOI: 10.1038/s42255-023-00931-7

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