Doubling down against diabetes: Turbo-charged gut hormones

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A collaboration between scientists in Munich, Germany and Bloomington, USA may have overcome one of the major challenges drug makers have struggled with for years: Delivering powerful nuclear hormones to specific tissues, while keeping them away from others.

The teams led by physician Matthias Tschöp (Helmholtz Zentrum München, and Technische Universität München) and chemist Richard DiMarchi (Indiana University) used natural gut peptides targeting cell membrane receptors and engineered them to carry small steroids known to act at the cell nucleus. DiMarchi and Tschöp hoped that such "turbo-charged" hormone hybrids would only deliver their steroid inside cells, where their specific peptide receptor was expressed at the surface.

Both teams had been working together for years to discover new ways to treat obesity and diabetes. They therefore started out with the gut hormone glucagon-like peptide-1, which is known to act at pancreas and brain cells to improve insulin secretion, blood glucose, and body weight. They engineered these peptides to reversibly bind the female sex steroid, estrogen, which is also known to confer powerful metabolic benefits at some of the same target cells. In the past, pharmacologists had been unable to utilize such benefits as high doses of systemic estrogen can also powerfully affect reproductive organs and increase cancer risk.

Using their GLP-1/estrogen-conjugates however, DiMarchi and Tschöp found that they were able to multiply metabolic benefits in mice, without apparent side effects on estrogen-sensitive reproductive organs such as

the uterus. They also found no impact of their "turbo-charged" gut peptides on growth of estrogen-sensitive tumors. Genetic studies at the same time however uncovered clear estrogen effects in pancreas and brain tissue of mice treated with the new combination drug candidate, indicating that the collaborating teams had indeed succeeded with targeted delivery of steroids.

"Our novel GLP-1/estrogen molecules seem to outperform more traditional therapeutics in mouse models of obesity and type 2 diabetes" says Brian Finan, scientist at the Helmholtz Zentrum München and first author of the study published online in the journal *Nature Medicine*. "What we are even more excited about" he adds "is the opportunity to use targeted steroid hormone for other diseases, where side effects had prevented therapeutic use in the past. "There is still a lot we don't know about the mechanistic details," cautions Matthias Tschöp, director of the Helmholtz Institute for Diabetes and Obesity "but if they proof safe enough for clinical use, these molecules could offer transformative potential."

More information: Finan B. et al. (2012) Targeted estrogen delivery reverses the metabolic syndrome. *Nature Medicine*, advances online publication, 11. November 2012. www.nature.com/nm/journal/vaop … nt/full/nm.3009.html

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