Tethering together type 2 diabetes drugs increases efficacy of combination therapy

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Biomedical engineers at Duke University have shown that the efficacy of a two-pronged type 2 diabetes treatment increases when the drugs are

linked by a heat-sensitive tether rather than simply concurrently administered. The combination molecule is formed by an elastin-like polypeptide (ELP) linker that forms a gel-like depot when injected under the skin, which slowly dissolves and releases the active drug over time.

This novel approach features the commonly prescribed type 2 diabetes drug glucagon-like peptide-1 (GLP-1) and the compelling drug candidate fibroblast growth factor 21 (FGF21) that together create tight glycemic control and potent weight-reduction in diabetic mice. Coupled with the slow-release function of the ELP, the effects last longer than one week with a single injection.

Because GLP-1, a short peptide, and FGF21, a large folded protein, are such different compounds, these findings suggest that this approach to combination drug design could be applied to disease therapies beyond diabetes.

The results appear online on August 26 in the journal *Science Advances*.

"In the burgeoning field of multi-functioning single-molecule diabetes drug design, researchers primarily unite drugs that are similar in size, structure and function," said Caslin Gilroy, a postdoctoral scholar at the University of California, Berkeley, who led the project while completing her Ph.D. in biomedical engineering at Duke. "Being able to combine such structurally distinct drugs into a single molecule while maintaining the bioactivity and stability of each is a big technological achievement."

Type 2 diabetes is a progressive disease where body tissues become resistant to the effects of insulin, which regulates the movement of sugar from the bloodstream into cells. When this carefully tuned system breaks down, blood sugar levels remain toxically elevated and a host of serious complications can follow. While many treatment options exist, a single

drug is rarely able to treat an advanced case. Conventional medications lose their potency over time and frequently cause weight gain, which itself can promote insulin resistance and exacerbate the disease.

A growing class of drugs is based on GLP-1, a naturally occurring peptide released from the intestines after a meal. GLP-1 therapy enhances the release of insulin from the pancreas while promoting weight loss. However, the high doses of GLP-1 that are sometimes necessary to maintain healthy blood sugar levels have been shown to cause gastrointestinal distress. Researchers are exploring combination therapies that strategically pair GLP-1 with additional drugs to maximize glucose control, minimize side effects and augment weight loss.

While most drug combinations incorporate small peptides from the same family as GLP-1, Gilroy and Ashutosh Chilkoti, the Alan L. Kaganov Distinguished Professor of Biomedical Engineering at Duke, chose to work with FGF21. A metabolic hormone, FGF21 regulates insulin sensitivity, energy expenditure and fat metabolism within body tissues.

"FGF21 functions through a different mechanism than GLP-1, and we hypothesized that the two drugs would complement each other nicely," said Gilroy. "GLP-1 increases insulin secretion by the pancreas, while FGF21 enhances the body's response to the insulin. GLP-1 reduces food intake, while FGF21 helps burn more calories."

But rather than simply injecting diabetic mice with both drugs at the same time, the researchers decided to link GLP-1 and FGF21 together into a single molecule. This approach to combination therapy has several advantages. A single molecule is more predictable in how it will disperse through the body, act on its target tissues and eventually be cleared. A single drug is also beneficial for the prescribing physician and patient, as it reduces the medication burden and simplifies the treatment regimen. And the FDA approval process for a single drug is more straightforward

than for a drug mixture.

GLP-1 and FGF21, however, are both peptide-based drugs, heavily reliant on shape and surface features to function. Tethering the two without interfering with either is easier said than done.

To form one drug out of two, the researchers turned to the ELP—a specialty of the Chilkoti research group. ELPs are chains of repetitive peptide sequences that are highly disordered in nature. This disorder provides flexibility, enabling drugs fused at each end of the ELP the room to do their respective jobs. The modularity of ELPs also make them highly tunable, allowing for the design of the best delivery system possible.

Peptide-based drugs suffer from two notable disadvantages; they have a short half-life, due to rapid clearance from the body, and they must be administered by needle. An ELP-based delivery platform, however, addresses both of these issues.

"Linking the drugs to an ELP allows us to design a compound that is liquid at room temperature but forms a gel-like depot upon injection," said Gilroy. "The depot dissolves over the course of at least a week, slowly and regularly releasing drug to the system over time."

Chilkoti already has two Phase II clinical trials underway using ELPs as slow-release delivery systems. One trial aims to treat pulmonary arterial hypertension, while the second involves a potential therapy for COVID-19.

In the study, after verifying that GLP-1 and FGF21 retain their respective functions and potencies when linked together by an ELP, Gilroy and Chilkoti tested their multi-functioning, slow-release molecule in a mouse model of diabetes.

The results show that levels of drug circulating in the system remained steady while blood sugar levels were brought down to a healthy level and maintained for up to 10 days following a single dosing. Mice treated with the GLP-1/FGF21 combination drug were better able to recover from a glucose challenge compared to either drug alone, and were the only test group to lose weight during the trial.

The drug combination also worked better when GLP-1 and FGF21 were tethered together rather than being delivered as a mixture of individual drugs. The researchers think that linking them guarantees that GLP-1 and FGF21 are always acting in concert at the same point in time, allowing their mechanisms of action to synergize and work together.

"We had speculated that we may see synergy when we combined GLP-1 and FGF-21 because they have different modes of action," said Chilkoti. "That was really just a hope at the outset of this project, and we were more than pleasantly surprised when Caslin showed that combining these drugs into a single molecule clearly showed a synergistic therapeutic effect compared to a mixture of the two drugs. The data is so compelling that we believe it's ready for a company to pursue this strategy commercially. Duke's Office of Licensing and Ventures is currently looking to license it."

More information: C.A. Gilroy et al, "Sustained Release of a GLP-1 and FGF21 Dual Agonist from an Injectable Depot Protects Mice from Obesity and Hyperglycemia," *Science Advances*, Aug. 26, 2020. DOI: 10.1126/sciadv.aaz9890 , advances.sciencemag.org/content/6/35/eaaz9890

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