

Team finds unique anti-diabetes compound using powerful new drug-discovery method

December 7 2015

Scientists from The Scripps Research Institute (TSRI) have deployed a powerful new drug discovery technique to identify an anti-diabetes compound with a novel mechanism of action.

The finding, which appeared online ahead of print in *Nature Communications*, may lead to a new type of diabetes treatment. Just as importantly, it demonstrates the potential of the new technique, which enables researchers to quickly find drug candidates that activate cellular receptors in desired ways.

"In principle, we can apply this technique to hundreds of other receptors like the one we targeted in this study to find disease treatments that are more potent and have fewer side effects than existing therapies. It has been a very productive cross-campus collaboration, so we're hoping to build on its success as we continue to collaborate on interrogating potential therapeutic targets," said Patricia H. McDonald, an assistant professor at TSRI's Jupiter, Florida campus and a senior investigator of the study.

McDonald's laboratory collaborated on the study with the laboratory of Richard A. Lerner, the Lita Annenberg Hazen Professor of Immunochemistry at TSRI's La Jolla campus, and with other TSRI groups. Lerner has pioneered techniques for generating and screening large libraries of antibodies or proteins to find new therapies.

In Search of a Better Activator

Three years ago, Lerner and colleagues devised a technique called autocrine selection, which enables scientists to screen very large libraries of molecules to find those that not only bind a given cellular receptor but also activate it to bring about a desired therapeutic effect. Since then, the Lerner laboratory and collaborating scientists have used the technique to find new molecules that block cold virus infection, boost red blood cell production and kill cancer cells, among other effects.

For the new study, Lerner and his laboratory used the technique to target a receptor linked to type 2 diabetes, a life-shortening disease estimated to affect 30 million people in the US alone.

The GLP-1 receptor, as it is known, is expressed by insulin-producing "beta cells" in the pancreas. Several drugs that activate this receptor—drugs called GLP-1 receptor agonists—are already approved for treating type 2 diabetes. In this case, the TSRI team's aim was to find a molecule that activates the GLP-1 receptor in a unique way.

The GLP-1 receptor belongs to a large class of receptors known as G protein-coupled receptors (GPCRs). Scientists recently have come to understand that when a molecule activates a GPCR, it doesn't necessarily trigger a single chain of biochemical signals within the cell. In fact, most GPCR agonists trigger signals via multiple distinct pathways—one being via a so-called G protein and another via a protein known as beta-arrestin. In some cases, a "biased agonist" that principally activates just one of these pathways would work better than one that activates both.

In this case, Lerner and his laboratory teamed up with McDonald, an expert on GPCRs and metabolic disease, to find a molecule that would preferentially activate the GLP-1 receptor's G protein pathway.

To start, researchers in Lerner's laboratory, including Hongkai Zhang, a senior staff scientist and co-first author of the study, generated a library of candidate molecules—based on a known GLP-1 receptor agonist, Exendin-4, a small protein (peptide) originally found in the venom of Gila monster lizards; a synthetic version of this protein is now used as a type 2 diabetes medication. Zhang created about one million new peptides by randomly varying one end of Exendin-4—the end that normally activates the G protein and beta arrestin pathways.

"The idea was that at least one of these many variants would induce a change in the shape of the GLP-1 receptor that would activate the G-protein pathway without activating the beta arrestin pathway," Zhang said.

Using the autocrine selection system, Zhang and colleagues rapidly screened these variant peptides and eventually isolated one, P5, that potently and selectively activated the GLP-1 receptor's G-protein pathway. An initial test in healthy mice showed that P5 worked well at boosting glucose tolerance—at about one-hundredth the dose of Exendin-4 needed for the same effect.

Protein expert Philip E. Dawson, an associate professor at TSRI's La Jolla campus, synthesized sufficient quantities of P5, and McDonald and her laboratory performed more advanced tests in cultured cells and in mice.

A Different Mechanism

Exendin-4 and other GLP-1 receptor agonists work in part by strongly stimulating [pancreatic beta cells](#) to produce more insulin—which signals muscle and fat cells to draw glucose from the blood, thus lowering blood glucose levels.

McDonald and her team found that although P5 equals or outperforms Exendin-4 in standard mouse models of diabetes, it stimulates insulin production only weakly.

"We didn't expect that, but in fact, it was a nice finding because less reliance on stimulating insulin could mean less stress on the [beta cells](#)," said Emmanuel Sturchler, staff scientist in the McDonald laboratory and co-first author of the study.

Investigating further, the team found that while the peptide doesn't make mice fatter or heavier, it triggers the growth of new fat cells. In typical obesity-related diabetes, fat cells grow larger, not more numerous, and as they grow larger, they lose their ability to respond to insulin (insulin resistance). The proliferation of [fat cells](#) with P5 was accompanied by signs of increased insulin sensitivity in those cells, suggesting that the peptide works in part by alleviating insulin resistance.

Exendin-4 induces a feeling of satiety, causing mice (and people) to modestly lower food intake and thus lose weight. But the researchers found that P5 lacks this mechanism and appears to have no effect on appetite or weight.

"P5's mechanisms of action turned out to be quite different from Exendin-4's, and we think that this finding could lead to new therapeutics," Sturchler said.

The team will now look for opportunities to develop P5 into a new diabetes drug. The researchers also see this as the first of many discoveries of GPCR-targeting compounds with unique and potentially valuable properties—as well as discoveries in basic GPCR biology.

More information: Hongkai Zhang et al. Autocrine selection of a GLP-1R G-protein biased agonist with potent antidiabetic effects,

Nature Communications (2015). [DOI: 10.1038/ncomms9918](https://doi.org/10.1038/ncomms9918)

Provided by The Scripps Research Institute

Citation: Team finds unique anti-diabetes compound using powerful new drug-discovery method (2015, December 7) retrieved 26 April 2024 from

<https://medicalxpress.com/news/2015-12-team-unique-anti-diabetes-compound-powerful.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.