

Wonder drug? Exploring the molecular mechanisms of metformin, a diabetes drug with Medieval roots

January 10 2020, by Delthia Ricks



Metformin 500mg tablets. Credit: public domain

At only pennies per dose, metformin is a Type 2 diabetes drug with distant roots in Medieval folk medicine and a powerful capacity to reduce body weight, fat mass, circulating glucose—and prevent the disorder altogether in people at elevated risk.

New research on the most widely prescribed Type 2 [diabetes drug](#) in the world arrives as a global obesity epidemic continues unabated. Obesity is the leading risk factor for Type 2 diabetes, a metabolic disorder.

While scientists have found that more than 60 percent of [metformin](#)'s ability to control Type 2 is derived from lowering [body weight](#), it has taken until now to tease out key molecular mechanisms underlying how the medication does its job.

In the United Kingdom, Dr. Stephen O'Rahilly and colleagues at the University of Cambridge, are in the vanguard of scientists worldwide who have tackled a series of metformin studies in humans and laboratory animals. The team has shown how the [drug](#) causes [weight loss](#), even among [heart patients](#) who don't have diabetes.

Outside of their work, other scientists are hailing metformin as a wonder drug not only because of its effect on Type 2 diabetes, but because of its emerging prominence in cancer research and potential influence in the lungs of those diagnosed with tuberculosis.

"Metformin was first used as a glucose-lowering drug in patients with Type 2 diabetes," O'Rahilly, a professor of clinical biochemistry and medicine, told Medical Xpress. "In these [patients], the weight loss can be quite modest, probably because when you reduce glucose in Type 2 diabetes, you stop calories being lost in the urine as sugar, and that works against the weight-reducing effects.

"It was only when long-term studies in non-diabetic participants were undertaken that it became clear that people who actually had good compliance with metformin lost on average around 6 percent of their body weight and could keep it off for years," added O'Rahilly, director of the Wellcome Trust-MRC Institute of Metabolic Science-Metabolic Research Laboratories.

Reporting in the journal *Nature*, O'Rahilly and his team explained the relationship between metformin and a key circulating protein, a molecule known as GDF15. The initials stand for growth and differentiation factor 15. The protein is a member of the TGF- β superfamily, a vast group of cell regulatory proteins.

GDF15 carries out a wide range of biological activities and is found in a variety of tissues, regulating apoptosis and cell repair. As it turns out, GDF15 plays a potent role in the presence of metformin toward controlling Type 2 diabetes.

The mutual relationship now has been fully elucidated by O'Rahilly and his team, and for the first time, posits the molecular mechanisms underlying the weight loss that occurs among patients on the drug. Metformin works with GDF15 and by itself to induce weight loss and maintain energy balance, the team found.

"Our data does suggest that most, if not all, of the weight loss effects of the metformin require GDF15. However, metformin continues to have some effects in lowering glucose and insulin that are independent of weight loss and independent of GDF15," O'Rahilly said.

The researchers found that "metformin treatment increases the levels [of GDF15] quite markedly in all people who take the drug regularly," O'Rahilly said.

He described metformin as the most widely prescribed diabetes medication on the planet. Known generically as metformin, the drug is sold under the brand name Glucophage. Sixty tablets cost about \$4 at prescription drug discounters, such as Walmart, in the United States.

Approved by the U.S. Food and Drug Administration in 1995, metformin had been widely prescribed for decades in Europe before it was finally given a green light in a country with more than 30 million Type 2 diabetics. The U.S. additionally has 84.1 million people with pre-diabetes, a condition that can lead to the full-blown disease.

Among medications, metformin has a long and storied past. The compound destined to become metformin was first isolated during the Middle Ages from the French lilac, a plant scientifically known as *Galega officinalis*. Ground flowers and leaves were administered by healers to patients suffering from constant urination, a hallmark of a disorder that later would become known as diabetes. The [active ingredient](#) in French lilac, a plant also called goat's rue, was identified hundreds of years later as galegine, which triggered a striking reduction in blood glucose.

By the 1950s, scientists were able to exploit folk medicine uses and develop the drug that became metformin. In recent years, in vitro studies by Dr. Lloyd Trotman at Cold Spring Harbor Laboratory in New York have shown metformin to be effective against prostate cancer cells. And in November, scientists in Mexico found that metformin promotes the destruction of *Mycobacterium tuberculosis* bacteria in the lungs. The drug enhances the activity of antimicrobial peptides known as β -defensins. The peptides are common in lung epithelial tissue and are active against Gram negative and Gram positive bacteria.

O'Rahilly and colleagues, meanwhile, have described the benefits of metformin in both human clinical trials and experiments involving

animal models. In both types of investigations, metformin influenced weight loss and GDF15 activity.

For example, in one of the human clinical trials cited in the *Nature* paper, the team measured circulating GDF15 and found that after two weeks on metformin, there was approximately a 2.5-fold increase in circulating GDF15. To determine if the increase was sustained, protein levels were measured six, 12 and 18 months. Patients who took metformin wound up losing about 3.5 percent of their body weight. In another trial, patients lost even more.

In wild-type mice, oral metformin also increased circulating GDF15. Protein levels additionally rose in the distal intestine and kidneys. Metformin prevented weight gain in response to a high-fat diet in the animals but not in mice lacking GDF15 or its receptor protein, GFRAL. Metformin had effects on both energy intake and energy expenditure that required GDF15, the team found.

O'Rahilly said the research has been reproduced by other teams assuring him and his colleagues that they have demonstrated how metformin lowers body weight.

"The key findings of our work have already been independently replicated by Greg Steinberg at McMaster University. We are indeed undertaking further studies to explore exactly where the GDF15 is coming from and how it is regulated," O'Rahilly said.

More information: Anthony P. Coll et al. GDF15 mediates the effects of metformin on body weight and energy balance, *Nature* (2019). [DOI: 10.1038/s41586-019-1911-y](https://doi.org/10.1038/s41586-019-1911-y)

Citation: Wonder drug? Exploring the molecular mechanisms of metformin, a diabetes drug with Medieval roots (2020, January 10) retrieved 29 April 2024 from <https://medicalxpress.com/news/2020-01-drug-exploring-molecular-mechanisms-metformin.html>

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