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# Old diabetes drug teaches experts new tricks

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Research from the Johns Hopkins Children's Center reveals that the drug most commonly used in type 2 diabetics who don't need insulin works on a much more basic level than once thought, treating persistently elevated blood sugar — the hallmark of type 2 diabetes — by regulating the genes that control its production.

Reporting in the May 15 issue of *Cell*, investigators say they have zeroed in on a specific segment of a protein called CBP made by the genetic switches involved in overproduction of glucose by the liver that could present new targets for drug therapy of the disease.

In healthy people, the liver produces glucose during fasting to maintain normal levels of cell energy production. After people eat, the pancreas releases insulin, the hormone responsible for glucose absorption. Once insulin is released, the liver should turn down or turn off its glucose production, but in people with type 2 diabetes, the liver fails to sense insulin and continues to make glucose. The condition, known as insulin resistance, is caused by a glitch in the communication between liver and pancreas.

Metformin, introduced as frontline therapy for uncomplicated type 2 diabetes in the 1950s, up until now was believed to work by making the liver more sensitive to insulin. The Hopkins study shows, however, that metformin bypasses the stumbling block in communication and works directly in the liver cells.

"Rather than an interpreter of insulin-liver communication, metformin

takes over as the messenger itself," says senior investigator Fred Wondisford, M.D., who heads the metabolism division at Hopkins Children's. "Metformin actually mimics the action of CBP, the critical signaling protein involved in the communication between the liver and the pancreas that's necessary for maintaining glucose production by the liver and its suppression by insulin."

To test their hypothesis, researchers induced insulin resistance in mice by feeding them a high-fat diet over several months. Mice on high-fat diets developed insulin resistance, and their high blood glucose levels did not drop to normal after eating. Once treated with metformin, however, CBP was activated to the levels of nondiabetic mice, and their blood glucose levels returned to normal. However, when given to diabetic mice with defective copies of CBP, metformin had no effect on blood glucose levels, a proof that metformin works through CBP.

Researchers further were able to determine that metformin worked on one particular section of CBP by studying the drug's effects in mice with normal CBP and in mice missing this section of their CBP. The mice with normal CBP responded to metformin with a drop in their fasting blood glucose — much like diabetes patients do — while the mice missing that section in their CBP had no decrease in their blood sugar.

Because CBP is involved in growth and development and a variety of metabolic processes in other organs, this newly discovered pathway may hold therapeutic promise for conditions like growth retardation, cancer and infertility, investigators say.

Another important finding in the study: Investigators have discovered a biomarker that can predict how well a person will respond to treatment with metformin and help doctors determine the optimal therapeutic dose, which can vary widely from person to person. The Hopkins team has found that in mice, metformin changes CBP in white bloods cells —

just as it does in liver cells — creating a molecular marker that is easily measured via a standard blood test.

"This is the quintessence of individualized medicine: We have found an easily obtainable biomarker with great predictive power that can tell us whether and how well an individual will respond to treatment and help us determine the best dose right away instead of trying to do it by trial and error," Wondisford says.

Researchers caution that, while promising, their findings must be first replicated in humans.

Diabetes (type 1 and type 2) is a leading cause of kidney failure, eye disease and amputations, and one of the main causes of heart disease and stroke. Nearly 24 million Americans have type 2 diabetes, according to the U.S. Centers for Disease Control.

Source: Johns Hopkins Medical Institutions