Study: Most-used diabetes drug works in different way than previously thought

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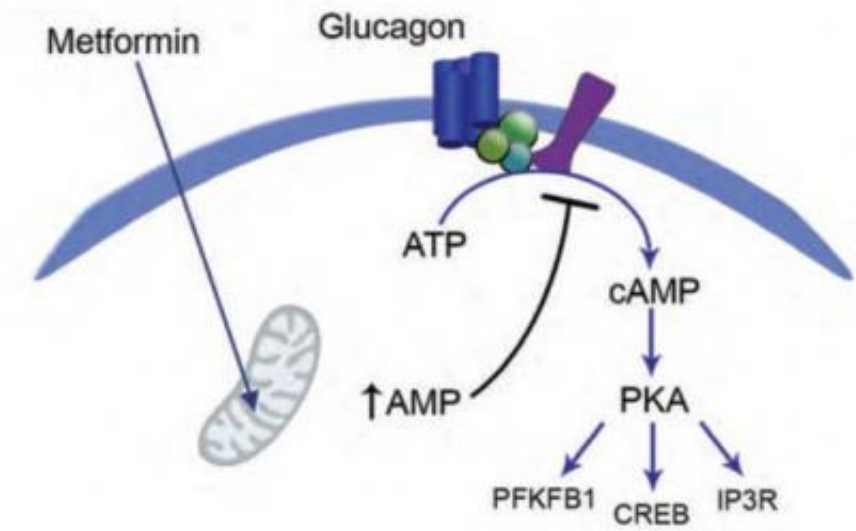

Proposed model: Metformin enters the cell and acts on the mitochondria, causing increased AMP. Elevated cellular AMP levels inhibit membrane bound adenylyl cyclase, causing a reduction in cellular cAMP levels and decreased PKA activation and target phosphorylation. Credit: Morris Birnbaum, M.D., Ph.D., Perelman School of Medicine, University of Pennsylvania; *Nature*

A team, led by senior author Morris J. Birnbaum, MD, PhD, the Willard and Rhoda Ware Professor of Medicine, with the Institute for Diabetes, Obesity, and Metabolism, Perelman School of Medicine, University of

Pennsylvania, found that the diabetes drug metformin works in a different way than previously understood. Their research in mice found that metformin suppresses the liver hormone glucagon's ability to generate an important signaling molecule, pointing to new drug targets. The findings were published online this week in *Nature*.

For fifty years, one of the few classes of therapeutics effective in reducing the overactive glucose production associated with diabetes has been the biguanides, which includes metformin, the most frequently prescribed drug for type 2 diabetes. The inability of insulin to keep liver glucose output in check is a major factor in the high blood sugar of type 2 diabetes and other diseases of insulin resistance.

"Overall, metformin lowers blood glucose by decreasing liver production of glucose," says Birnbaum. "But we didn't really know how the drug accomplished that."

Imperfectly Understood

Despite metformin's success, its mechanism of action remained imperfectly understood. About a decade ago, researchers suggested that metformin reduces glucose synthesis by activating the enzyme AMPK. But this understanding was challenged by genetic experiments in 2010 by collaborators on the present Nature study. Coauthors Marc Foretz and Benoit Viollet from Inserm, CNRS, and Université Paris Descartes, Paris, found that the livers of mice without AMPK still responded to metformin, indicating that blood glucose levels were being controlled outside of the AMPK pathway.

Taking another look at how glucose is regulated normally, the team knew that when there is no food intake and glucose decreases, glucagon is secreted from the pancreas to signal the liver to produce glucose. They then asked if metformin works by stopping the glucagon cascade.

The Nature study describes a novel mechanism by which metformin antagonizes the action of glucagon, thus reducing fasting glucose levels. The team showed that metformin leads to the accumulation of AMP in mice, which inhibits an enzyme called adenylate cyclase, thereby reducing levels of cyclic AMP and protein kinase activity, eventually blocking glucagon-dependent glucose output from liver cells.

From this new understanding of metformin's action, Birnbaum and colleagues surmise that adenylate cyclase could be a new drug target by mimicking the way in which it is inhibited by metformin. This strategy would bypass metformin's affect on a cell's mitochondria to make energy, and possibility avoid the adverse side effects experienced by many people who take metformin, perhaps even working for those patients resistant to metformin.

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