CLINICAL IMPLICATIONS OF BASIC RESEARCH

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The Target of Metformin in Type 2 Diabetes

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In the crowded firmament of antihyperglycemic agents, the biguanide metformin is the brightest star. Metformin features as first-line pharmacologic treatment for type 2 diabetes in virtually all guidelines and recommendations, its efficacy and tolerability are well tested, and it is safe and cheap. In use in Europe since the late 1950s and reintroduced into the North American market two decades ago, metformin is by far the most widely used antidiabetic drug, alone or in combination with other antihyperglycemic agents. Unlike the sulfonylureas and insulin, metformin is not associated with weight gain or hypoglycemia; it is quite friendly to patients.

But its mode of action has been very difficult to pinpoint. In animals and humans, metformin is absorbed through the upper small intestine, is concentrated in enterocytes and hepatocytes, circulates essentially unbound, and is eliminated, unchanged, by the kidneys.[1] At the whole-body level, metformin itself does not affect insulin sensitivity in muscle or adipose tissue[2] but consistently reduces endogenous glucose production by inhibiting gluconeogenesis.[1] Proposed mechanisms of action have included delayed intestinal glucose absorption, enhanced release of glucagon-like peptide 1, augmented lactate production by enterocytes, and activation of AMP-activated protein kinase in hepatocytes consequent to decreased energy charge, as well as inhibition of glucagon signaling, glycolytic enzymes, transcription of gluconeogenic enzymes, or mitochondrial complex I (which is made up of NADH and a reductase) (Fig. 1). This plethora of explanations has emerged from studies performed with the use of a variety of techniques, time frames, and metformin concentrations.

In a series of comprehensive experiments, Madiraju and colleagues[3] have used intravenous infusions of metformin in the rat to show that concentrations within the therapeutic range acutely reduce endogenous glucose production and plasma glucose levels and raise plasma lactate and glycerol levels, without changing hepatic gluconeogenic gene expression or cellular energy charge. Furthermore, the results compellingly demonstrate that metformin selectively inhibits the mitochondrial isoform of glycerophosphate dehydrogenase, an enzyme that catalyzes the conversion of glycerophosphate to dihydroxyacetone phosphate (DHAP), thereby transferring a pair of electrons to the electron transport chain (Fig. 1). The result is a reduction in cytosolic DHAP and a rise in the cytosolic NADH–NAD ratio, which restrains the conversion of lactate to pyruvate; the use of glycerol and lactate as gluconeogenic precursors therefore drops, and glycerol and lactate levels build up in the plasma. Long-term metformin dosing reproduced these reciprocal changes in the redox state, which is decreased in the mitochondrion and increased in the cytoplasm.[3]

Does the elucidation of this mechanism mean that the search is over? Almost certainly, not only because the supporting evidence included important control experiments[3] but also because the proposed molecular mechanism is primary, simple, and elegant, as well as being compatible with ancillary (e.g., the release of glucagon-like peptide 1) or secondary (e.g., the abatement of glucose toxicity) mechanisms.

Among the best drugs are those — such as statins and, more recently, sodium–glucose cotransporter 2 inhibitors (e.g., dapagliflozin) — that inhibit a single key enzyme or transporter in a pathway. Agents that have an effect on molecular master switches (e.g., thiazolidinediones) open the door to unpredicted off-target side effects, which may limit their clinical use.

Does the new basic science change the clinical landscape? Probably not in the short term, but there are aspects of metformin treatment that

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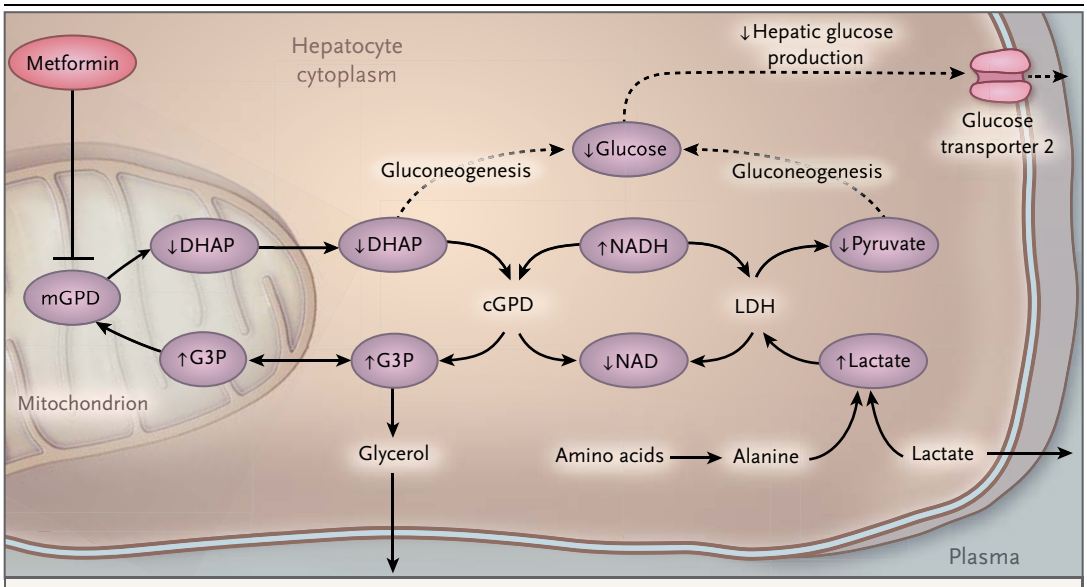

Figure 1. How Metformin Suppresses Hepatic Gluconeogenesis: A Model.

A recent study by Madiraju et al.[3] suggests that metformin suppresses gluconeogenesis by inhibiting a mitochondrion-specific isoform of glycerophosphate dehydrogenase (mGPD). This, in turn, decelerates the dihydroxyacetone phosphate (DHAP)–glycerophosphate shuttle (glycerophosphate is also called glycerol-3-phosphate [G3P]). As a result, the ratios of G3P to DHAP, NADH to NAD, and lactate to pyruvate all increase in the cytoplasm. Gluconeogenesis decreases, and therefore secretion of glucose by the hepatocyte decreases, and excess levels of glycerol and lactate are released into the plasma. The term cGPD denotes the cytoplasmic isoform of glycerophosphate dehydrogenase, and LDH lactate dehydrogenase.

might benefit from a better understanding of its mode of action. Are the gastrointestinal side effects of metformin linked with its target in enterocytes?[4] Are the effects on blood lipids (a slight reduction in low-density lipoprotein cholesterol) and on liver fat accumulation in line with the molecular changes detected in the liver? Are there reproducible, independent effects of metformin on beta-cell function in patients with diabetes? If metformin blocks an enzyme, why do some patients not have a response in spite of having few or no side effects? Why do patients have secondary treatment failure (at an estimated rate of approximately 15% per year in clinical practice[5])? Does this reflect disease progression — as many believe — or tachyphylaxis? In the latter case, can response be restored with intermittent insulin treatment? Why has it been so hard to develop additional metformin-like agents?

New clinical research is now more likely to arise from this old drug. In the clinic, doctors can answer the kind of question that patients, back from browsing the Web, increasingly pose:

"Doc, how is this pill supposed to help me?"

"Sir, it blocks an enzyme that makes the liver put out too much sugar into your blood."

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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1. Bailey CJ, Turner RC. Metformin. N Engl J Med 1996;334:574-9.
2. Natali A, Baldeweg S, Toschi E, et al. Vascular effects of improving metabolic control with metformin or rosiglitazone in type 2 diabetes. Diabetes Care 2004;27:1349-57.
3. Madiraju AK, Erion DM, Rahimi Y, et al. Metformin suppresses gluconeogenesis by inhibiting mitochondrial glycerophosphate dehydrogenase. Nature 2014;510:542-6.
4. Bailey CJ, Wilcock C, Scarpello JHB. Metformin and the intestine. Diabetologia 2008;51:1552-3.
5. Brown JB, Conner C, Nichols GA. Secondary failure of metformin monotherapy in clinical practice. Diabetes Care 2010;33:501-6.

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