Role of the Gut in the Glucose-lowering Effects of Metformin

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ABOUT METFORMIN

Metformin is the most widely prescribed drug to treat patients with type 2 diabetes mellitus (T2D) and was added to the World Health Organization's list of essential medicines in 2011. Major benefits of metformin include improved glycemic profile and reduced cardiovascular-associated mortality, with a safety/side effect profile that distinguishes metformin from other anti-diabetic drugs. Even with its widespread use, how metformin achieves its anti-diabetic effects has baffled the scientific community for decades.

Metformin (1,1-dimethylbiguanide) is an orally administered drug that was first introduced as part of the biguanide class in the late 1950s. It is a highly polar and cationic molecule that is poorly absorbed in the gastrointestinal tract, with nearly half of ingested metformin accumulating in the gut mucosa of the distal small intestine at 30-300 times its plasma concentration[1]. Despite metformin's low absorption, its pharmacological effects were largely attributed to action in the liver, where it was presumed to target enzymes like hepatic AMPK to suppress glucose production. The role of AMPK was supported by *in vitro* experiments that used concentrations (> 1 mM) far exceeding its circulating levels in patients (10-40 uM)[2].

From a PK/PD perspective, therefore, the liver can only be part of the story. The action of metformin in the gut has recently become more fully characterized. Whole-body imaging data using glucose tracers highlight the role of the gut in metformin-mediated systemic glucose disposal, and the molecular and bacterial players potentially responsible for metformin's gut effects are now being identified. With this revised mechanistic understanding, improved strategies to deliver metformin to its key site of action can be developed, so that patients currently unable to receive metformin might receive this foundational therapy. In this white paper, we will summarize the data which re-frames our thinking about metformin's various mechanisms and inform use in broader patient populations for glycemic control.

CLINICAL EXPERIENCE POINTING TOWARD THE GUT

Human data supports a revised model wherein metformin enhances whole-body glucose disposal in T2D patients significantly via the gut. In early clinical experience with metformin, intravenous delivery had no acute glucose lowering effects in T2D patients, whereas subsequent studies where metformin was dosed orally or directly infused into different regions of the small intestine showed effective glucose-lowering effects[3,4]. The distinct pharmacology imparted by intravenous versus oral/lumenal delivery of metformin suggests that high concentrations of metformin in the gut are required for glucose disposal. Very recently, PET/CT imaging was used to confirm the gut-targeted biodistribution of metformin in humans[5].

Real-world clinical practice also identified the gut as a major site of metformin-mediated glucose disposal. Radiation oncologists frequently use a non-metabolized version of glucose called 18-fluorodeoxyglucose (FDG) to visualize tumors in cancer patients. Patients taking metformin, however,

are instructed to discontinue metformin prior to FDG-utilizing procedures because high intestinal uptake of FDG induced by metformin obscures proper tumor visualization in the gastrointestinal tract. Significant bowel uptake of FDG and subsequent excretion in the lumen induced by metformin has been documented in several independent studies[6].

EMERGING MOLECULAR MECHANISMS

What specific mechanism(s) in the gut might be responsible for metformin's effects?

One potential mechanism involves duodenal AMPK activation[7]. Intraduodenal metformin infusion in mice activates intestinal AMPK and significantly reduces HGP, an effect not observed when metformin is infused into the portal vein. Moreover, the effect on HGP is lost when AMPK is genetically ablated or chemically inhibited. Duodenal AMPK activation also increases the glucose transporter Glut2 on the basolateral membrane[8]. Glut2 is then able to move glucose from plasma into the gut lumen, reducing levels of glucose in systemic circulation. Duodenal AMPK activation also leads to increased thermogenesis in brown adipose tissue and improved whole body energy expenditure, presumably via alterations in the gut microbiome[9]. Collectively, duodenal AMPK activation is potentially a key contributor to the overall therapeutic effects of metformin.

Metformin may also induce changes in gut microbiota independent of duodenal AMPK action. Human clinical studies have shown that metformin treatment in naïve type 2 diabetics leads to increased growth of *B. adolescentis*, a gut microflora shown to improve insulin sensitivity in rodents with metabolic syndrome[10]. Metformin treatment in humans also leads to the accumulation of bile acids such as glycoursodeoxycholic acid (GUDCA) [11]. GUDCA increases the production of GLP-1, which stimulates insulin secretion, inhibits glucagon secretion, and could contribute to a portion of metformin's glucose-lowering effects.

GUT CHECK

Assigning the exact contribution of each gut- and non-gut mechanism may be an impossible task, and it is quite likely that multiple pathways collaborate to achieve metformin's glucose-lowering effects. However, clinical data with a delayed-release formulation of metformin (called metformin DR) build more evidence in support of the gut contribution to metformin's pharmacology. Delayed-release metformin restricts dissolution until the lower gastrointestinal tract, leading to high intestinal exposure of metformin and 60% less in systemic circulation. Despite lower levels of drug in circulation, metformin DR elicits significant HbA1c reduction in T2D patients (>0.6% after 16 weeks in a Phase 2 trial)[12]. These correlative data – that 60% less systemic drug exposure recapitulates most of metformin's glucose-lowering effect – support the working model of the gut being a significant contributor to the overall pharmacology of metformin. Occam's razor at least elevates the gut as a primary site of action for metformin.

OUTLOOK

Understanding a drug's mechanism is more than a scientific curiosity, as unravelling the underlying pharmacology can point to new drug targets or ways to use current medications. In the case of metformin, an improved understanding of the gut's role has inspired the development of a formulation that maximizes gut exposure and minimizes systemic levels. This new delivery strategy can potentially expand the use of metformin where its use is restricted due to safety concerns from high systemic concentrations. For instance, metformin is contraindicated in patients with advanced chronic kidney

disease (CKD) due to the risk of metformin accumulation inducing lactic acidosis. Furthermore, although metformin is used 'off-label' in gestational diabetes, evidence suggests that fetal metformin exposure via the maternal circulation is harmful. In these populations, metformin DR is anticipated to provide glucose-lowering benefits without high systemic metformin concentrations. Clinical trials testing metformin DR in both groups will soon be underway.

Additional mechanistic work is needed to clarify the gut effects of metformin. While recent imaging work has sharpened focus on the gut as a major site of metformin-mediated glucose disposal, a carefully designed assessment of mass balance might better quantitate the relative contribution of the gut and other metabolic tissues. Meanwhile, continued work on identifying the various targets of metformin, both in the gut and beyond, may lead to the discovery of novel agents that may approach the benefit offered by metformin throughout its 60 years of clinical use.

ENDNOTES

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