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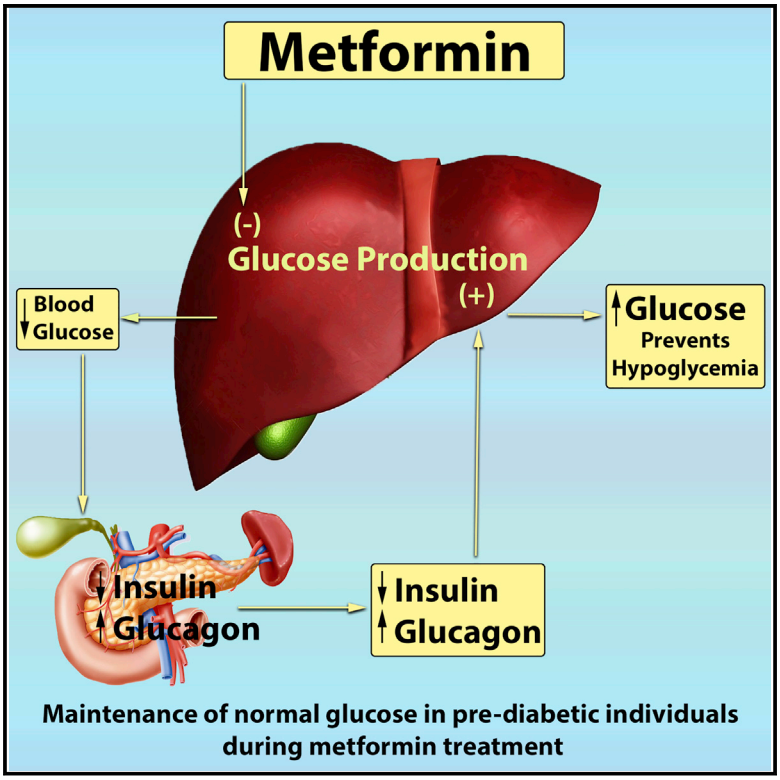
Hyperglucagonemia Mitigates the Effect of Metformin on Glucose Production in Prediabetes

Graphical Abstract



Highlights

- Metformin does not inhibit glucagon-stimulated glucose production
- Increased glucagon prevents hypoglycemia during metformin therapy
- Metformin therapy reduces glucogenic precursors
- Metformin counteracts the catabolic effects of glucagon

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In Brief

Using a randomized, double-blinded, placebo-controlled, crossover study design in prediabetic individuals, Konopka et al. show that metformin improves fasting and postprandial glycemia without inhibiting glucagon-stimulated glucose production as reported in preclinical studies. During metformin therapy, increased glucagon and decreased glucogenic precursors may maintain glucose production to prevent hypoglycemia.

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Report

Hyperglucagonemia Mitigates the Effect of Metformin on Glucose Production in Prediabetes

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SUMMARY

The therapeutic mechanism of metformin action remains incompletely understood. Whether metformin inhibits glucagon-stimulated endogenous glucose production (EGP), as in preclinical studies, is unclear in humans. To test this hypothesis, we studied nine prediabetic individuals using a randomized, placebo-controlled, double-blinded, crossover study design. Metformin increased glucose tolerance, insulin sensitivity, and plasma glucagon. Metformin did not alter average basal EGP, although individual variability in EGP correlated with plasma glucagon. Metformin increased basal EGP in individuals with severe hyperglucagonemia (>150 pg/ml). Decreased fasting glucose after metformin treatment appears to increase glucagon to stimulate EGP and prevent further declines in glucose. Similarly, intravenous glucagon infusion elevated plasma glucagon (>150 pg/ml) and stimulated a greater increase in EGP during metformin therapy. Metformin also counteracted the protein-catabolic effect of glucagon. Collectively, these data indicate that metformin does not inhibit glucagon-stimulated EGP, but hyperglucagonemia may decrease the ability of the metformin to lower EGP in prediabetic individuals.

INTRODUCTION

The biguanide metformin is the most commonly prescribed oral anti-hyperglycemic agent, consumed annually by over 150 million people worldwide. Despite metformin's efficacy in lowering blood glucose and decreasing the incidence of type 2 diabetes mellitus (T2DM) (Knowler et al., 2002), its mechanisms of action remain incompletely understood. In T2D individuals, metformin lowers blood glucose by decreasing endogenous glucose production (EGP) (DeFronzo et al., 1991; Hundal et al., 2000; Musi et al., 2002; Stumvoll et al., 1995). Subsequent work demonstrated that metformin acted to inhibit EGP by activating AMP-activated protein kinase (AMPK) (Shaw et al., 2005; He et al., 2009). However, metformin reduced EGP in AMPK knockout mice, challenging the notion that AMPK is required for decreased EGP by metformin (Foretz et al., 2010). However, these authors utilized supra-pharmacologic doses of metformin, and Cao et al. (2014) subsequently demonstrated that pharmacologic doses of metformin could indeed inhibit hepatic gluconeogenesis. Metformin was also recently discovered to decrease glucagon-induced glucose production (Miller et al., 2013) and diminish the use of gluconeogenic metabolites for glucose production by altering mitochondrial glycerophosphate dehydrogenase and the cellular redox status in the liver (Madiraju et al., 2014). Moreover, metformin was recently shown to impart decreased fasting glucose and hepatic glucose production through the intestines (Duca et al., 2015; Buse et al., 2016). Therefore, several lines of evidence suggest that metformin lowers EGP by independent or perhaps combined mechanisms that change rate-limiting gluconeogenic enzyme levels (He et al., 2009; Foretz et al., 2010), decrease glucagon action (Miller et al., 2013), or limit the conversion of gluconeogenic substrates (e.g., lactate, alanine, amino acids [AAs]) to glucose (DeFronzo et al., 1991; Madiraju et al., 2014; Stumvoll et al., 1995).

Although preclinical models have provided clues regarding how metformin may elicit its therapeutic effect, translating these mechanisms to the clinical situation has been difficult because many studies have used supra-pharmacologic dosing schemes and biguanide derivatives contraindicated for human use (He et al., 2009; He and Wondisford, 2015). Furthermore, metformin may also influence glucogenic precursors and insulin sensitivity through its influence on amino acid kinetics, a possibility that has yet to be explored in humans. Therefore, we investigated whether metformin, at therapeutic doses, would inhibit glucagon-stimulated EGP and AA kinetics in humans. We conducted a randomized, placebo-controlled, double-blinded crossover study in prediabetic individuals and measured EGP and AA kinetics using stable isotope methodology under basal, glucagon-deficient, and glucagon-stimulated conditions.

RESULTS AND DISCUSSION

Nine participants completed the study (physical characteristics are shown in Table S1). Seven had a family history of T2DM, and eight were metformin-naive. One participant had previously