LIVER

Novel molecular mechanism proposed for hepatic metformin activity

Patients with type 2 diabetes are often prescribed metformin for the treatment of hyperglycemia. Until now, the metformin-induced decrease in hepatic glucose production was thought to be mediated via the LKB1/AMP-activated protein kinase (LKB1/AMPK) pathway and subsequently inhibition of gluconeogenesis. Foretz and colleagues have challenged this belief by demonstrating that both AMPK and LKB1 are dispensable for the inhibition of hepatic glucose production by metformin.

The researchers monitored glucose production and gluconeogenic gene expression in hepatocytes isolated from mice lacking both catalytic subunits of hepatic AMPK or LKB1, in the presence and absence of metformin. They found an increase in the metformin-induced inhibition of hepatic glucose production in both AMPK-deficient and LKB1-deficient heptocytes—this inhibition correlated with a dose-dependent reduction of intracellular ATP content. In addition, glucose production and gluconeogenic gene expression was found to be normal in AMPK-deficient hepatocytes.

"We showed that metformin inhibits hepatic glucose production through a mechanism linked to a decrease in the hepatic energy charge rather than a direct inhibition of gluconeogenic gene expression," explains Foretz. "Our results contribute to a growing body of data indicating that the development of small molecules targeting mitochondrial function in the liver, thus causing a moderate variation in hepatic energy charge, is an attractive therapeutic strategy for the treatment of type 2 diabetes."

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Original article Foretz, M. *et al.* Metformin inhibits hepatic gluconeogenesis in mice independently of the LKB1/AMPK pathway via a decrease in hepatic energy state. *J. Clin. Invest.* **120**, 2355–2369 (2010)