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Metformin reverses FOXO3-induced hyperactivation of hepatic gluconeogenesis and catabolic pathways

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Diabetes mellitus type 2 is a complex metabolic disorder characterized by high glucose levels and insulin resistance. Currently, metformin is the most widely used anti-diabetic drug that suppresses hepatic glucose production, but the underlying molecular mechanism is not clearly understood. FoxO transcription family members represent key downstream targets of insulin and growth factors regulating energy metabolism. Interestingly, a member of the FoxO family, FOXO3 genotypes are associated with insulin sensitivity phenotypes and longevity in human, suggesting that FOXO3 is a critical factor for metabolic control. However, the direct correlations between FoxO3 and insulin resistance remained still elusive. The goal of this study was to elucidate the hepatic role of FoxO3 in energy metabolism and Diabetes mellitus type 2. Gain-of-function studies were conducted with transgenic mice expressing a constitutively active FOXO3 in hepatocytes. Here we demonstrate that FOXO3 is a key regulator of hepatic glucose and lipid metabolism in transgenic mice. FOXO3 activation led to progressive hepatic atrophy in the absence of significant inflammation. Up-regulation of gluconeogenesis-associated genes, loss of hepatocyte glycogen stores and activation of lipid catabolism were noted. Animals showed elevated blood glucose and insulin levels as well as impaired insulin sensitivity. Strikingly, FOXO3-induced metabolic alterations were completely reversed after treatment with metformin. Despite the wide acceptance of metformin as first-line therapy for diabetes, the molecular mechanisms of action remain incompletely understood. Given that our model depends on the expression of a FoxO3 transcription factor that was rendered non-responsive to insulin signaling (insulin resistance) suggests that this terminal step is crucially targeted by metformin. Our findings identify FoxO3 as a critical metabolic regulator and a likely hepatic target of metformin.

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Effects of *Dillenia indica* on carbohydrate digestion and absorption, hepatic glycogen and serum lipids in type 2 diabetic rats

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Dillenia indica was previously reported to have hypoglycemic activity in type 2 diabetic rats. In this study, the possible mechanism of hypoglycemic action of the fruit was elucidated in type 2 rats. Antihyperglycemic effect was evaluated at different prandial states and time points by measuring serum glucose and insulin. Insulin secretory effect was evaluated in isolated rat islets. Sucrose malabsorption was evaluated in six different parts of GI tract. To evaluate glucose absorption in gut, an *in situ* intestinal perfusion technique was used. Disaccharidase activity was measured by incubating extract and sucrose with disaccharidase enzyme extracted from rat intestine. Effect on starch digestibility was determined as a function of time in a fiber-enzyme-starch mixture system using dialysis membrane. Extract showed significant hypoglycemic activity ($p<0.05$) in postprandial state following glucose administered without significantly increasing insulin level. Extract did not induce any insulin secretion from islets in presence of glucose (3 mM and 11 mM). Extract significantly inhibited the absorption of glucose ($P<0.05$) during perfusion of gut. It significantly suppressed postprandial hyperglycemia after sucrose ingestion ($p<0.01$) and reversibly increased unabsorbed sucrose content throughout gut ($p=0.05$-0.01). Extract significantly lowered serum glucose ($p<0.05$), Cholesterol ($p<0.05$), TG ($p<0.05$) and increased hepatic glycogen ($p<0.05$) without increasing body weight in 28 days study (0.5 g/kg, twice daily). The extract also inhibited both intestinal disaccharidase and alpha-amylase ($p<0.01$). Hypoglycemic activities of *D. indica* are associated with inhibition of carbohydrate digestion and absorption in the gut and enhancement of glucose uptake in the liver.

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