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TITLE

## Hepatic a Typical PKC: A Novel Target for Newly-develpoed Inhibitors that Reverse Obesity and Metabolic Syndrome and Diabetic Characteristics and Features in Human Hepatocytes and a Murine Obesity/Diabetes Model

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**Aims/Hypothesis:** We tested the role of the hepatic protein kinase C-ι (PKC-ι) in mediating metabolic abnormalities in type 2 diabetes mellitus (T2DM) with novel PKC-ι inhibitors.

**Methods:** We examined insulin signalling in hepatocytes of non-diabetic and T2DM humans, and effects of two newly developed small molecule PKC-ι/λ inhibitors in both human hepatocytes and a murine obesity/T2DM model.

**Results:** Opposite to PKC-ι deficiency in muscle, which limits glucose transport, PKC-ι was over-expressed/over-active in hepatocytes of T2DM humans, and accompanied by increased expression of sterol receptor element binding protein-1c (SREBP-1), SREBP-1c-dependent lipogenic enzymes, and proinflammatory and gluconeogenic enzymes. Moreover, apparently acting via conserved levels and heightened phosphatidylinositol-3-kinase activity of insulin receptor substrate(IRS)-2, insulin increased hepatic PKC-ι expression by a PKC- ι-(i.e., self)-dependent, i.e., feed-forward/positive-feedback, mechanism. In contrast, Akt2 activation was diminished in human T2DM hepatocytes, most likely reflecting diminished IRS-1 levels and activity. Treatment of T2DM hepatocytes with two novel PKC-ι/λ inhibitors diminished aPKC activity and expression of lipogenic, proinflammatory and gluconeogenic enzymes. Also, in a murine obesity/T2DM model, both agents selectively inhibited hepatic PKC-ι/λ and abnormalities in hepatic expression of lipogenic, proinflammatory and gluconeogenic enzymes, thereby improving insulin signalling in muscle and adipocytes, insulin resistance, glucose intolerance, hepatosteatosis, abdominal obesity, hypertriglyceridemia and hypercholesterolemia.

**Conclusions/interpretations:** PKC-ι is overexpressed/overactive in an insulin-driven cycle in hepatocytes of T2DM humans and accompanied by multiple lipid and carbohydrate abnormalities that are effectively overcome by liver-selective PKC-ι inhibitors. Our findings highlight the pathological importance of this aberrant signalling pathway and suggest inhibition of PKC-ι as potential therapy.