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Effect of Metformin on Insulin Signal Transduction and Expression of Phosphoenolpyruvate Carboxykinase in cultured Hepatoma Cells

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Metformin is an oral antihyperglycemic agent used in the management of type 2 diabetes mellitus. Its antidiabetic effect is mainly a consequence of reduced hepatic glucose production (gluconeogenesis) and increased insulin-stimulated glucose uptake in peripheral tissues. Although the liver is now widely accepted as the major site of metformin action, the molecular basis for metformin's effect on hepatocytes is largely unknown. Hepatic insulin resistance in type 2 is associated with impaired insulin signaling downstream of its receptor, This involves disturbed insulin signaling towards the suppression of PEPCK expression as the key enzyme within the regulation of gluconeogenesis. The present study aimed to investigate (1) the effect of metformin on PEPCK expression in cultured hepatocytes, (2) to determine whether the antidiabetic action of metformin in hepatocytes is associated with effects on signaling protein expression and phosphorylation, and (3) to determine whether observed effects of metformin on hepatocytes differ between normal and insulin resistant states.

The present data demonstrated: (1): Therapeutic concentrations of metformin can inhibit basal PEPCK mRNA expression and also decrease cAMP- and dexamethasone-induced PEPCK gene expression through interaction with insulin. (2): Insulin and metformin

can inhibit PEPCK gene expression via different mechanisms. (3): Under normal conditions, therapeutic concentrations of metformin have no significant effect on insulin signal transduction via IRS1, IRS2 and PI3-kinase. (4): Chronic insulin exposure of HepG2 cells results in downregulation of insulin signal transduction via both the PI3-kinase and MAP-kinase pathway. (5): Therapeutic concentrations of metformin largely reverse the effects of chronic hyperinsulinism on amount and activation of insulin signaling molecules. (6): Pharmacological concentrations of metformin can inhibit insulin signal transduction both under normal conditions and in the insulin resistant state induced by chronic hyperinsulinism.

In conclusion, these findings suggest that the inhibitory effect of metformin on hepatic gluconeogenesis are associated with a decrease in PEPCK gene expression. The effects of metformin on insulin signaling suggest that enhancement of insulin signal transduction could represent a primary mechanism of metformin action in insulin resistant type 2 diabetics.