

Pancreatic beta cell function and gene changes in animal diabetes

studies with the histone acetyltransferase protein TIP60, isosteviol and soy protein

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ABSTRACT

Abnormal beta cell function during insulin resistance is recognized as a key factor for the development of type 2 diabetes (T2DM). We aimed at gaining insight into the pathogenesis of T2DM by studying changes in genes involved in glucose sensing, transcription factors regulating insulin expression and beta cell function. Subsequently, we wanted to explore if the insulinotropic compound isosteviol and isolated soy protein do influence islet cell gene expression and the intermedian metabolism in the type 2 diabetic KKA γ mice.

The cytosolic phospholipase A₂ (cPLA₂), that is expressed in β -cells, hydrolyzes the sn-2 binding of glycerophospholipids and liberate arachidonic acid (AA), an important effector of glucose stimulated insulin secretion (GSIS). We demonstrated that the histone acetyltransferase protein TIP60 is an important co-repressor of TEL-mediated transcriptional repression. TIP60 interacts with cPLA₂ α and potentiates cPLA₂ mediated AA production. The function of cPLA₂ in β -cells is potentially interesting since it generates AA that regulates the GSIS. Thus Tip60 may be critically involved in β -cell function and pathophysiology.

We hypothesize that Tip60 in β -cells regulates the glucose stimulated insulin secretion in the normal and diabetic state via binding to and regulation of cPLA₂. Tip60 influence the insulin sensitivity and the susceptibility to developing T2DM. Therefore we studied the expression of TIP60 in isolated islet from normal and diabetic mouse (C57BL/6J vs KKA γ) as well as clonal Min-6 and INS1 β -cells. Furthermore, we transiently over-expressed TIP60 in MIN-6 and INS1 cells and generated stable TIP60 expressing clones of INS1 using retro viral transduction followed by investigation of the effect on glucose stimulated insulin secretion.

We have previously demonstrated that stevioside, an analog of isosteviol, possesses insulinotropic and antihyperglycemic properties. Here we investigate the effect of isosteviol and soy bean protein isolate with at high isoflavone content in the obese T2DM model mice KKA γ . Three groups of KKA γ mice was for nine weeks given either a standard chow diet, chow with isosteviol (20 mg/kg BW/day) or 50% chow + 50% soy protein.

After treatment fasting plasma glucose, insulin, triglycerides and cholesterol were measured as well as genes involved in glucose sensing, transcription factors regulating insulin expression and β -cell function were explored using relative real time RT-PCR and micro arrays.

The present study demonstrates that TIP60 expression is not dys-regulated in diabetic KKA γ mice compared to normal C57 mice, as well as transient and stable over expression of TIP60 in the INS-1E

cell line do not affect GSIS. Furthermore, we found that isosteviol and soy protein isolate improve glucose and insulin sensitivity as well as improving the lipid profile and up-regulates the gene expression of key β -cell genes, including insulin regulatory transcription factors.