The role of regulator of calcineurin 1 (RCAN1) in the regulation of glucose homeostasis

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Regulator of calcineurin 1 (RCAN1) is a gene located on chromosome 21 and is over expressed in the brains of Down syndrome (DS) patients. Our lab has previously shown that RCAN1 regulates exocytosis in adrenal chromaffin cells. As the incidence of diabetes is 5-10 times greater in the DS population we are investigating the effect of increased RCAN1 expression and its possible role in the pathogenesis of diabetes. Transgenic mice with a universal over-expression of RCAN1 were generated for this study. *In vivo* studies indicate that transgenic mice develop age-dependent diabetes characterized by increased fasting blood glucose levels of 5.8±0.3 mmol/L (n=9) at 60 days old compared to 4.2±0.2 mmol/L (n=9) in age-matched wild-type mice ($p<0.05$). Glucose tolerance, measured by injecting 2mg glucose/g body weight, is also reduced in transgenic mice, with glucose values reaching peak levels of 27.5±1.4 mmol/L (n=5) after 60 minutes compared to 19±1.3 mmol/L (n=5) in wild-type mice ($p<0.01$). Immunohistochemical analysis of pancreatic islets revealed that transgenic mice have a 70% reduction in islet area (n=4) at 100 days. Electron microscopy analysis reveals that transgenic mice have a 40% increase in empty secretary vesicles (n=3) at 120 days. Transgenic mice also have significantly decreased fasting blood insulin values at 120 days (n=6) when compared to age-matched wild-type mice. In islets of transgenic mice, expression of genes such as those mutated in hereditary forms of monogenic type 2 diabetes (MODY) and others related to β-cell survival and insulin production were downregulated. Our findings highlight a novel role of RCAN1 in regulating glucose homeostasis, islet growth, secretary vesicle loading and insulin release. Additionally expression of RCAN1 increased 2.5 fold ($p<0.05$) when islets were exposed *in vitro* to 16.7 mM glucose for 6 days. This along with our previous findings provide the exciting proposition that RCAN1 may be involved in the β-cell failure and hypoinsulinemia that occurs in the later stages of type 2 diabetes.