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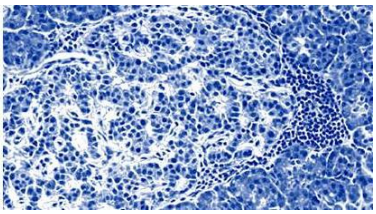

Loss of Carboxypeptidase E in Pancreatic Beta Cells Does Not Accelerate the Development of Obesity-induced Glucose Intolerance in Mice

AUTHORS

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PURPOSE

Carboxypeptidase E (CPE) is an enzyme essential in the processing of neuroendocrine peptide precursors to functional hormones. Human and mice lacking *CPE* have elevated levels of plasma proinsulin, become obese, and progress towards severe diabetes through undefined mechanisms. We aimed to determine whether the lack of *CPE* in pancreatic βcells contributes to the development of diabetes.

METHODS

We generated β-cell specific-*Cpe* knockout (β*Cpe*KO; *Ins1*$^{cre/+}$ x *Cpe*$^{fl/fl}$) mice, and analyzed their β-cell area, islet insulin granule distribution, insulin secretion dynamics, and plasma insulin- and proinsulin-like immunoreactivity. In addition, we fed both male and female β*Cpe*KO and Wt (*Cpe*$^{fl/fl}$) mice a low-fat or high-fat diet (10% or 45% total energy) for 24 weeks, and monitored their weight gain, fasting plasma glucose levels, insulin sensitivity, and glucose tolerance.

SUMMARY OF RESULTS

Both male and female β*Cpe*KO mice, on a regular chow diet, have ~2 fold increased beta cell area, ~20-fold elevation in serum proinsulin-like immunoreactivity, and a markedly increased proportion of immature secretory granules in islet beta cells. Interestingly, insulin secretion dynamics (assessed by glucose-stimulated insulin secretion in a perifusion system) are similar between β*Cpe*KO and *Wt* islets, suggesting that impaired granule maturation does not impact exocytosis. Mature (fully processed) insulin levels were also similar between β*Cpe*KO and *Wt* mice in islet lysates (analyzed by western blotting and mass spectrometry), indicating the presence of compensatory mechanisms that enable complete proinsulin processing in the absence of Cpe. When placed on a high-fat diet for 24 weeks, β*Cpe*KO mice do not show accelerated development of weight gain or glucose intolerance compared to *Wt* littermates, suggesting that secretory stress induced by insulin resistance cannot unmask an impact on glucose homeostasis in mice with beta cell *Cpe* deficiency.

CONCLUSIONS
Our data suggest that, despite having elevated propeptide-processing burden, murine beta cells are able to produce mature insulin without Cpe. Loss of β-cell CPE function is likely not the sole contributor to diabetes in humans and mice carrying loss-of-function *CPE* mutations.