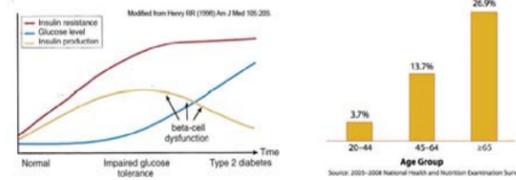


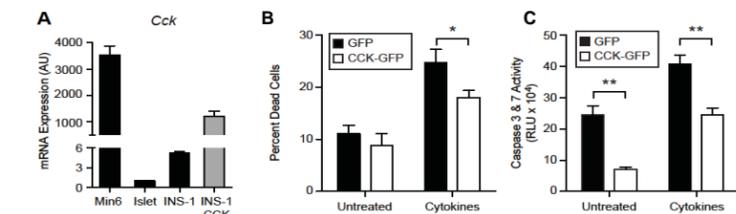
Introduction

- Type 2 diabetes develops when the pancreatic beta-cells are unable to compensate for increased insulin resistance.
- Insulin resistance increases with age, putting the elderly population at increased risk for type 2 diabetes.
- Cholecystikinin (CCK) is a gut hormone released in response to nutrient intake.
- CCK is produced by pancreatic islets under settings of insulin resistance and obesity.
- CCK-deficient obese mice have increased beta-cell death and develop diabetes.

Hypothesis
Islet-derived CCK acts locally to protect beta-cells from stress-induced death.

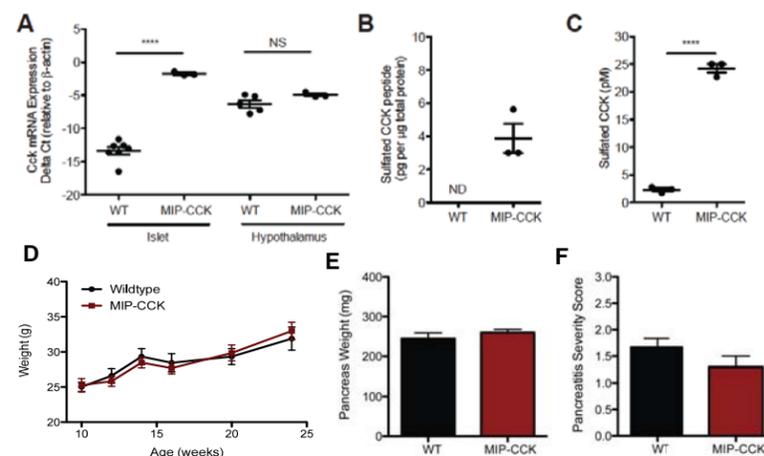


Overexpression of CCK protects INS-1 beta-cells from cytokine-induced death



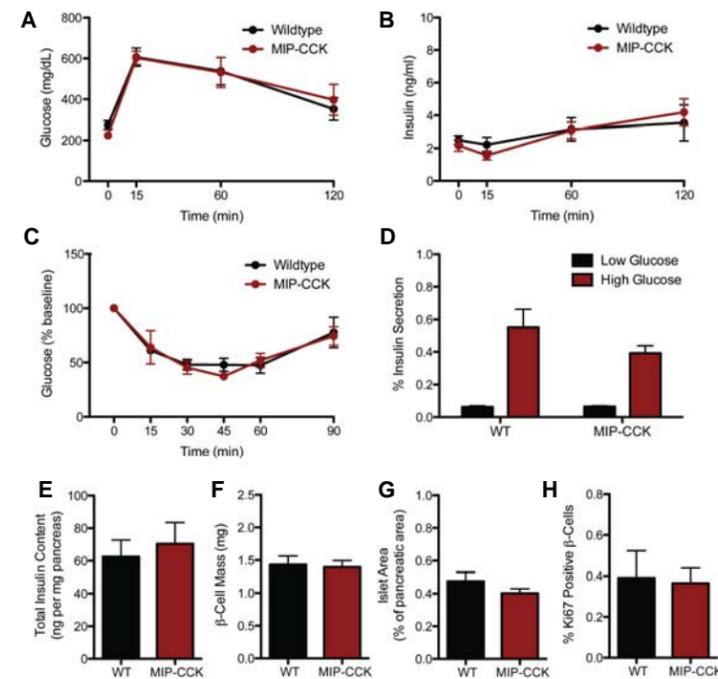
Cck mRNA expression levels differ in MIN6 and INS-1 cell lines, lean mouse islet (Islet), and INS-1 cells infected with GFP-CCK adenovirus (INS-1 CCK) (A). INS-1 cells treated with Ad-CCK-GFP had reduced cytokine-induced cell death (B) and caspase 3 and 7 activity (C).

MIP-CCK mice have increased islet-derived CCK without systemic effects



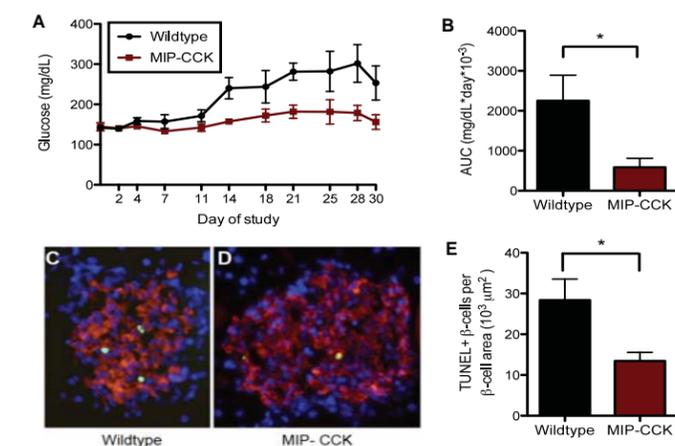
Cck mRNA expression is increased in MIP-CCK islets and unchanged in hypothalamus compared to wildtype (WT) controls (A). Islet CCK protein expression (B) and CCK secretion (C) are increased in MIP-CCK islets compared to controls. Body (D) and pancreas (E) weights do not differ between MIP-CCK and controls. There is no evidence of pancreatitis in MIP-CCK mice (F).

Young MIP-CCK mice do not have altered glucose homeostasis or beta-cell mass



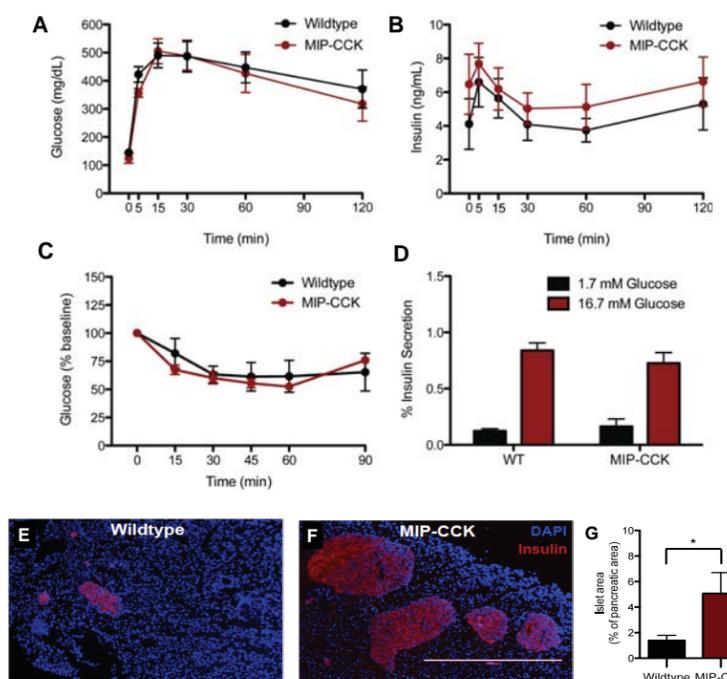
Glucose (A) and insulin (B) levels are not different from controls during a glucose tolerance test (IP-GTT). Insulin tolerance (IP-ITT) (C) and glucose-stimulated insulin secretion (D) also do not differ from controls. There is no difference in total insulin content (E), beta-cell mass (F), fractional islet area (G), or beta-cell proliferation as measured by Ki67 immunostaining (H).

MIP-CCK mice are protected from STZ



Random fed plasma glucose (A) and area under the curve analysis (B) demonstrate that MIP-CCK mice are resistant to STZ-induced hyperglycemia. Wildtype (C) and MIP-CCK (D) pancreata were stained for DAPI (blue), insulin (red), and TUNEL (green). Quantitative analysis (E) reveals reduced beta-cell death in MIP-CCK mice.

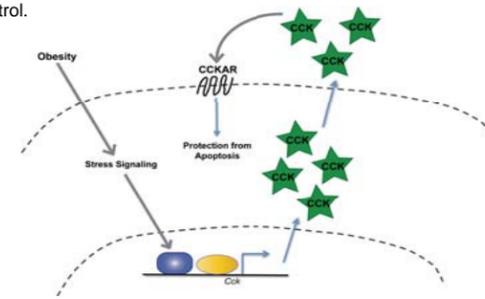
Aged MIP-CCK mice have normal glucose homeostasis and increased islet area



Glucose (A) and insulin (B) levels are not different from controls during a glucose tolerance test (IP-GTT). Insulin tolerance (IP-ITT) (C) and glucose-stimulated insulin secretion (D) also do not differ from controls. Wildtype (E) and MIP-CCK (F) pancreata were immunostained for insulin (red) and DAPI (blue). Quantitative analysis revealed increased fractional islet area in MIP-CCK pancreata (G).

Conclusions

- Local CCK production in the islet appears to act in a paracrine fashion to protect against beta-cell death under stress conditions such as obesity, STZ, and aging.
- CCK does not show effects on islet area or function in young, lean animals where stress and cell death levels are low.
- Under settings of increased cell death, such as STZ, CCK is able to protect beta-cells and prevent the onset of diabetes.
- In aging, CCK may protect beta-cells from death over the course of many years resulting in increased islet area and elevated plasma insulin levels in aged animals.
- CCK directed therapies could have multiple positive effects that would lead to improved diabetes control.



Funding Acknowledgements

Institute of Aging T32, NIDDK, Wisconsin Partnership Program, UW-Madison Department of Medicine