Cholecystokinin Protects Pancreatic Beta-Cells From Stress-Induced Cell Death

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Cck mRNA expression is increased in MIP-CCK islets and unchanged in hypothalmus compared to wildtype (WT) controls (A). Islet CCK protein expression (B) and CCK secretion (C) are increased in MIP-CCK 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).

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 proliferation as measured by Ki67 immunostaining (F).

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.