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

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Aged MIP-CCK phenotype

CCK may protect from ER stress

Conclusions

Background

• 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.
• Cholecystokinin (CCK) is a gut hormone released in response to nutrient intake.
• CCK is highly upregulated in pancreatic islets of obese mice.
• CCK deficient obese mice have reduced beta-cell mass and hyperglycemia due to increased beta-cell death.
• Isolated islets from CCK deficient obese mice are more susceptible to stress-induced cell death.

Aged male MIP-CCK mice have increased insulin levels and islet area, but normal glucose (not shown) and pancreatic histology. Non-fasted plasma insulin (A, n=4-14) from wildtype and MIP-CCK male mice from 10 to 40 weeks of age. Area under the curve analysis for plasma insulin (B, n=4-9). There is no evidence of pancreatitis (E) in aged (57-65 weeks) MIP-CCK mice relative to wildtype controls (n=5-6). Wildtype (C) and MIP-CCK (E) pancreata from 12-15 month old mice were immunostained for DAPI (blue) and insulin (red). Quantitative analysis demonstrated increased islet area (D) and average islet size (F) in MIP-CCK mice (n=7).

CCK may protect from ER stress in vitro and in vivo. Exogenous treatment with a CCK-8 analog (100nM) reduces the level of cleaved caspase-3 (A-B) in INS-1 cells treated for 4 hours with tuf thapsigargin (TD) (n=2). Beta-cell specific overexpression of CCK modestly improves hyperglycemia in Akita heterozygous males at 22 weeks of age (C) (n=2-3).

Conclusions

• CCK is expressed and secreted from pancreatic islets and beta-cell lines.
• Aged MIP-CCK mice have mildly increased insulin levels and increased islet area and islet size.
• Aged MIP-CCK mice have normal glucose levels and no evidence of pancreatitis.
• Beta-cell specific overexpression of CCK protects mice from STZ-induced beta-cell death and diabetes.
• CCK may protect beta-cells from ER stress-induced cell death.
• CCK is necessary and sufficient to protect from stress-induced beta-cell death.
• Local CCK production in the beta-cell appears to act in a paracrine fashion to protect against beta-cell death.
• CCK directed therapies could have multiple positive effects that would lead to improved diabetes control.

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