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REDUCED BASAL INSULIN SECRETION FROM ISLETS ISOLATED FROM TAFAZZIN DEFICIENT MICE IS ASSOCIATED WITH REDUCED MITOCHONDRIAL FUNCTION AND INCREASED EXPRESSION OF EXTRACELLULAR MATRIX PROTEINS

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Background:
Tafazzin is a transacylase which alters the content and molecular structure of cardiolipin (CL) in the inner mitochondrial membrane. The enzymatic machinery responsible for oxidative respiration are localized to the inner mitochondrial membrane and require CL for activity. As a result, tafazzin is critical for maintaining mitochondrial function. In beta cells, which are the insulin secreting cells of pancreatic islets, mitochondrial function is intimately linked to insulin secretion.

Objective:
Therefore, our objective was to determine whether tafazzin deficiency influences insulin secretion.

Methods:
We used whole pancreas and isolated islet preparations from 4-month-old male tafazzin knock-down and wildtype mice. We ascertained that beta cell number was similar between tafazzin knock-down and wild-type mice.

Results:
Ex vivo insulin secretion under non-stimulatory low glucose concentrations was reduced (52%) from islets isolated from tafazzin knock-down mice. Consistent with this, tafazzin knock-down mice exhibited reduced fasting plasma insulin levels. Mitochondrial oxygen consumption under low glucose conditions was also reduced (58%) in islets from tafazzin-deficient animals. To determine if the inhibitory effect was mediated in part by fatty acids, islets were treated with etomoxir, an inhibitor of mitochondrial fatty acid oxidation. Under low glucose conditions, etomoxir elevated mitochondrial respiration (5-fold) in islets from tafazzin knock-down mice, and lacked any effect on wild-type islets. The altered mitochondrial function identified in tafazzin knock-down islets was not associated with reduced CL content or elevated oxyCL species. RNA-Seq of isolated islets showed that tafazzin-deficiency increased expression of extracellular matrix genes which are linked to pancreatic fibrosis, activated stellate cells and impaired beta cell function.

Conclusion:
Our data indicates a novel role for tafazzin in regulating normal beta cell function, particularly under low glucose conditions.