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Investigating the molecular and metabolic regulators of insulin secretion

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Background:

Manitoban Indigenous youth are disproportionately affected by type 2 diabetes (T2D), a condition resulting from β cell failure. The exact mechanisms underlying β cell failure in T2D remain elusive. In recent years, environmental conditions associated with disruption of circadian rhythms have shown to augment susceptibility to T2D. Healthy β cells secrete insulin in a rhythmic manner to maintain glucose homeostasis. We have previously shown that the mitochondrial uncoupling protein, Ucp2, is rhythmically expressed over 24 hours and is an important regulator of diurnal insulin secretion capacities; however, the molecular regulators of diurnal Ucp2 expression/activity need to be investigated.

Objective:

We, **hypothesize**, that the circadian clock drives *Ucp2*expression and controls daily cycles of insulin secretion.

Methods:

BMAL1, a core component of the circadian clock machinery, was silenced in MIN6 clonal β cells by *Bmal1*siRNA to create a cellular model of circadian dysfunction. Using these cells, the impact on *Ucp2*mRNA expression and insulin secretion capacity were assessed over 24 hours. ATP and ROS levels were also quantified over 24 hours as they are important signals that regulate insulin secretion

Results:

*Bmal1*knockdown impaired rhythmic insulin secretionby chronically increasing*Ucp2* expression (2.4-fold). *Ucp2* upregulationwas associated with reduced ATP production over 24hrs, indicative of chronically increased mitochondrial uncoupling. Changes in rhythmic ATP and ROS levels correlated with altered rhythmic insulin secretion.

Conclusion:

The circadian clock regulates daily cycles of *Ucp2*expression in MIN6 cells, which is a part of an important metabolic switch needed to align time-of-day insulin secretion capacity with 24hr glucose tolerance. T2D treatments must account for daily cycles of insulin secretion to fully restore pancreatic function in the diabetes state. In future, we will generate β cell-specific *Bmal1*knockout mice to examine the impact of these cycles in whole animals.

Conclusion:

Preliminary results suggest that communities with COHI do not have significantly lower rates of dental surgery to treat S-ECC. However, including other known risk factors of S-ECC in further statistical analyses will help to determine whether COHI leads to lower rates of surgery under general anesthesia.