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First Author: Mason Poffenbarger
Brigham Young University
Nutrition, Dietetics and Food Science BYU ESC S-243 Provo, UT 84602
United States
Phone: 8014229082
mason.poffenbarger@gmail.com

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Sponsor: Jeffery Tessem
Sponsor Phone: 8014229082
jeffery_tessem@byu.edu
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Molecular Mechanisms of Beta Cell Adaptation to Hyperlipidemia

Mason C. Poffenbarger¹, Daniel R. Lathen¹, H. Austin Ricks¹, Andrew M. Barlow¹, Zoey F. Roth¹, Benjamin T. Bikman², Jeffery Sivert Tessem³. ¹Nutrition, Dietetics and Food Science, ²Physiology and Developmental Biology, Brigham Young University, Provo, UT, ³Brigham Young University, Provo, UT

Type 2 diabetes is characterized by hyperglycemia, hyperlipidemia and beta cell failure. Studies have shown that beta cells are extremely sensitive to hyperlipidemia, showing that short term cultures with elevated concentration of palmitate results in high levels of cell death. Though these studies demonstrate the toxic nature of palmitate on the beta cell, they do not accurately model the environment in which beta cells are exposed to elevated free fatty acids. We have, therefore, cultured the 832/13 beta cell line in progressively increasing levels of palmitate to determine the physiological and molecular changes that occur as beta cells adapt to this toxic environment. While 832/13 beta cells cultured immediately in 0.5mM palmitate result in severe cell death and failure to grow, 832/13 beta cells that are cultured in progressively increasing levels of palmitate (at 0.15mM, 0.3mM and 0.5mM palmitate) shows improved, although still impeded, proliferation rates. Culture in the progressively increasing concentrations causes downregulation of the beta cell transcription factors Nkx6.1 and Sox9, the glucose transporter Glut2, and the orphan nuclear receptors Nr4a1 and Nr4a3. Furthermore, as 832/13 beta cells are cultured for prolonged periods in elevated palmitate we observe downregulation of Nr4a target genes involved in mitochondrial respiration such as Idh3a, Idh3b, Idh3g, Dld and Dst. These changes correspond with modulation of mitochondrial respiration, and progressive deterioration of glucose stimulated insulin secretion, as well as decreased insulin content. These data begin to define the molecular changes that occur to the pancreatic beta cell as it is exposed to progressively increasing concentrations of palmitate, as is observed in type 2 diabetes disease progression.

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