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DISSERTATION

"HFD Dysregulates Hormone-Mediated Ca^{2+} Signaling in Hepatocytes"

by

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M.D./Ph.D. Program

B.E. 2014, The Cooper Union for the Advancement of Science and Art, New York, NY

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Abstract

The obesity epidemic is an escalating public health concern. Nonalcoholic fatty liver disease (NAFLD) is a common comorbidity of obesity that in severe cases requires liver transplant. NAFLD is associated with abnormalities in hormone signaling in hepatocytes, including a well-characterized resistance to insulin and an emerging picture of glucagon resistance. Animal models of NAFLD have revealed abnormalities in the homeostasis and signaling behavior of Ca2+, a diverse second messenger that in hepatocytes is a major driver of glucose production. We generated a model of short-term high fat diet (HFD) feeding to explore the timeline of NAFLD development, and found that only 1 week of HFD feeding was sufficient to significantly disrupt hormone-mediated Ca2+ signaling.

We used single-cell and population Ca2+ imaging to characterize the nature of this hormone insensitivity in detail. Hepatocytes characteristically exhibit regularly spaced repetitive spikes in cytosolic [Ca2+] in the presence of continuous hormone stimulation. We developed computational techniques to quantitatively analyze these Ca2+ oscillations, and found that short-term HFD slowed the kinetics of individual Ca2+ spikes and reduced the robustness of cellular responses. We determined that this reduced sensitivity was most likely the result of impaired inositol trisphosphate (IP3) production, while finding that endoplasmic reticulum Ca2+ homeostasis and the IP3 receptor were unaffected.

Further, we characterized the effect of short-term HFD on intercellular Ca2+ signaling. We developed a mouse model expressing GCaMP6f selectively in hepatocytes so that we could perform intravital imaging with a confocal laser scanning microscope. Normally, hormone-evoked intercellular Ca2+ waves are an important part of mustering an organ-wide response to a stimulus. In the intact HFD liver, the ability of norepinephrine (NE) to evoke Ca2+ signaling was reduced, and asynchronous firing of cells was observed rather than coordinated intercellular Ca2+ waves. Functionally, this resulted in reduced hepatic production of glucose in response to NE stimulation. We present a significant pathological change in cellular signaling behavior induced by short-term HFD feeding that predates any overlying disease. At this stage, there is no significant hepatic steatosis, no obesity, and no dyslipidemia, although there are some signs of insulin resistance. We propose that these changes in signaling behavior may in fact contribute to the development of liver pathology, perhaps via compensatory mechanisms that further impair hepatocyte function. These findings may offer a target for development of therapies intended to prevent the onset of NAFLD rather than treat existing disease.