Liver-Specific SIRT1 Knockout Mice Are Susceptible Diet-induced Obesity and Insulin Resistance and Decrease Whole Body Energy Expenditure

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BACKGROUND

- The recent epidemic of obesity and its associated conditions, such as diabetes, has increased the demand for novel therapeutics targeted toward modulating energy metabolism. The search for clinically useful drugs has thus far met with limited success, so that the identification of novel potential targets remains of great interest.
- ER stress has been implicated in the pathophysiology of type 2 diabetes (TZDM) (Ozcan, L., et al. Science, 2004).
- Previous studies have shown the therapeutic effects of SIRT1 activation on TZDM (Finkel, T., et al. Nature, 2009; Li, Y. et al. FASEB J, 2011).

ABSTRACT

Although SIRT1 has been demonstrated to have therapeutic effects on metabolic deterioration in TZDM, the precise mechanisms by which SIRT1 improves insulin resistance remain unclear. Previous studies in Dr. Zang’s laboratory have indicated that SIRT1, an NAD-dependent deacetylase, regulates hepatic lipid metabolism through activation of AMPK. Dr. Zang’s laboratory recently demonstrated that adenosine-mediated overexpression of SIRT1 in the liver of diet-induced insulin-resistant low-density lipoprotein receptor-deficient mice and of genetically obese ob/ob mice attenuates hepatic steatosis and ameliorates systemic insulin resistance. Because the mammalian target of rapamycin complex 1 (mTORC1) and ER stress are hyperactive in obesity and type 2 diabetes, the primary goal of this project was to test whether the absence of SIRT1 in the liver induces mTORC1 activity and reduces energy expenditure in a diet-induced obese mouse model by the use of liver-specific SIRT1 deficient mice (SIRT1 LKO).

AIM

To determine whether the absence of SIRT1 in liver may lead to hepatic activation of mTORC1 and ER stress, which contributes to the development of diet-induced obesity, insulin resistance, and energy imbalance.

METHODS

Research Design and Groups

- Control (WT)
  - High Fat High Sucrose Diet (HFHS diet)
  - 5 mice

- Experimental (SIRT1 LKO)
  - HFHS Diet + Resveratrol (130 mg/kg/day)
  - 5 mice

Experimental Procedure and Endpoints

- Body Weight
- Food Intake: WT and SIRT1 LKO mice were placed in individual cages, and food intake was monitored over 24 hours for one week.
- Body Composition: was measured using the nuclear magnetic resonance (NMR) system with a Body Composition Analyzer Echo 900 (Echo Medical Systems). Body fat, lean mass, body fluids, and total body water were measured in live conscious mice with ad libitum access to chow.
- Energy Metabolism was determined by a comprehensive lab animal metabolic monitoring system (CLAMS). Mice of both genotypes were individually housed,acclimated to respiratory chambers for 24 h, and allowed free access to food or water. The data for oxygen consumption (VO2), carbon dioxide production (VCO2), and locomotor activity were simultaneously recorded over a 48-h period which was divided into a 24-h feed and a 24-h fast. VO2 and VCO2 were expressed as average values measured every 15 min over a 12-h block in the light and dark cycles.
- Glucose Tolerance Tests

The Animal Protocol of Diet-induced Obesity and Type 2 Diabetes

- Week 0: Control Diet
  - High Fat High Sucrose Diet
- Week 9: Sacrifice

Nuclear Magnetic Resonance (NMR) System

- Complementary Lab Animal Monitoring System (CLAMS)

Glucose Injection for Glucose Tolerance Test

- Time after Glucose Injection (min)

RESULTS

No Significant Difference in Food Intake Is Evident between Wild-Type and SIRT1 LKO Mice

- Daily Food Intake (g)

- Percentage Change in Body Weight (g)

- No Significant Changes in Daily Food Intake

- SIRT1 LKO Mice Are More Susceptible to HFHS Diet-induced Obesity

- SIRT1 LKO Mice Abrogate the Effect of Resveratrol to Reduce Body Weight Gain in Response to HFHS Diet

- Energy Expenditure

- Oxygen Consumption (VO2) Is Decreased in SIRT1 LKO Mice Fed a HFHS Diet During the Light and Dark Cycles

- Whole-body Energy Expenditure Is Significantly Decreased in HFHS-fed SIRT1 LKO Mice

- No Significant Changes of Physical Activity in HFHS-fed SIRT1 LKO Mice

CONCLUSIONS

- Liver-specific SIRT1 knockout mice after the HFHS challenge are prone to obesity, accompanied by increased total body weight gain and fat mass, but no changes in lean mass.
- The decreased total energy expenditure is the primary cause of induced adiposity in SIRT1 LKO mice fed a HFHS diet.
- Liver-specific SIRT1 knockout mice are susceptible to diet-induced glucose intolerance.
- Resveratrol diminishes diet-induced obesity and disrupts glucose homeostasis in a SIRT1-dependent mechanism.
- Future studies will investigate whether mTORC1 activation and ER stress contribute to the mild obesity and insulin resistant phenotypes seen in SIRT1 LKO mice.