Loss of Carnitine Palmitoyltransferase-2 in Skeletal Muscle results in Muscle Remodeling and Tissue-specific Sensitivity to Insulin in...

Introduction

The skeletal muscle is responsible for “90% of the insulin-stimulated glucose uptake, thus its susceptibility to insulin resistance is critical for glucose homeostasis.” Perturbed muscle metabolism of fatty acids is a common feature of obesity and insulin resistance and is associated with impaired insulin action. However, the role of muscle fatty acid oxidation (MFAO) in the etiology of obesity-related insulin resistance remains debated. We hypothesize that excessive muscle fatty acid oxidation is causal in diet-induced obesity and insulin resistance. To test this, we have generated a novel mouse model with impaired mitochondrial long-chain fatty acid oxidation by deleting Carnitine Palmitoyltransferase-2 (Cpt2) specifically in the skeletal muscle.

Carnitine Palmitoyltransferase-2 (CPT2) is a ubiquitous enzyme located in the inner mitochondrial membrane. It is a key component of the carnitine palmitoyltransferase system which imports long-chain fatty acids (LCFAs) into the mitochondria for beta-oxidation. Because there is only one known isoform of CPT2, and because LCFAa are the major fraction of FAA supplied to target tissues, CPT2 deficiency significantly impacts fatty acid-derived energy production.

1. CPT2 Deficiency in the Skeletal Muscle Prevents High Fat Diet-induced Obesity

Fasting blood glucose were determined in both Cpt2+/+ or Cpt2−/− mice after 1 week on a high fat (HF) or a low-fat diet (LF). Glucose Tolerance Test (ITT) was performed at week 15 (A) and Insulin Tolerance Test at week 16 on the diet (B). Tissue-specific insulin sensitivity was assessed via Akt phosphorylation at Ser473 in skeletal muscle (C) and liver (D) and pGSK3β, total GSK3β, total Akt and total pAkt in muscle (E) and liver (F). Data are presented as the mean ± S.E.M. n=12-15 for panels A and B, C, n=6 for panels D, E, F, p<0.05 * LF vs HF, p<0.05 ** LF vs HF, p<0.05 *** LF vs HF.

2. CPT2 Deficiency in the Skeletal Muscle Differentially Modulates Insulin Sensitivity

Figure 2. Muscle-specific CPT2 deficiency differentially modulates insulin sensitivity at tissue and whole-body levels.

3. CPT2-deficient skeletal muscle have a unique lipid profile

Conclusion

- We have generated a novel mitochondrial-FAD-deficient mouse model (Cpt2−/−) that is severely resistant to high-fat diet (HFD)-induced obesity. After 16 weeks of high-fat feeding, Cpt2−/− mice have 94% reduction in white adipose tissue mass, have overall preserved muscle mass and are protected against HFD-induced hepato- and cardiomyopathy.
- Indirect calorimetry showed that HFD-fed Cpt2−/− mice have increased Energy Expenditure which might contribute to the observed leanness.
- Cpt2−/− mice have lower basal glycemia and differential insulin sensitivity across different tissues. While liver and adipose tissue of Cpt2 knockout mice display a pronounced Akt hypophosphorylation under basal conditions, skeletal muscle retains normal p-Akt levels, suggesting that other peripheral tissues might be sparing glucose for skeletal muscle usage.
- CPT2 deficient muscles undergo significant remodeling in a tissue type dependent manner. Muscles with high content of oxidative fibers, like Soleus, seem to be more susceptible to long-chain acylcarnitine accumulation, increased mitochondrial content and altered substrates/FuT preferences. Despite these adaptive attempts, fatty acid deficient muscles have compromised function as evidenced by reduced general fatigue.

References and Acknowledgements


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