Report

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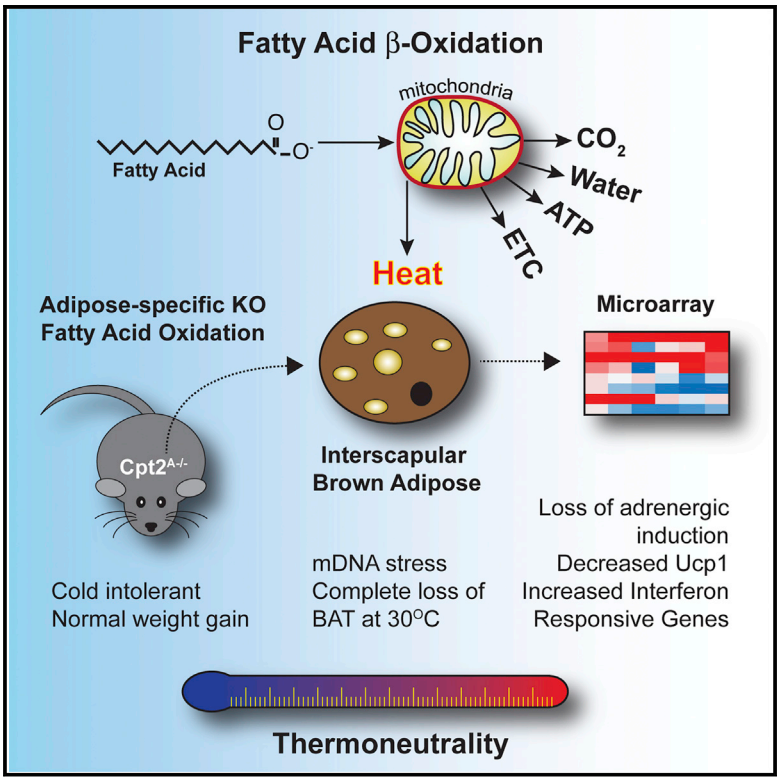
Loss of Adipose Fatty Acid Oxidation Does Not Potentiate Obesity at Thermoneutrality

Graphical Abstract



Highlights

- Fatty acid oxidation (FAO) is required for the induction of *Ucp1* and *Pgc1α* in BAT
- Increasing ambient temperature potentiates defects in FAO-deficient BAT
- Loss of adipose FAO induces mtDNA stress in BAT
- Loss of adipose FAO does not alter body weight or adiposity at thermoneutrality

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In Brief

Lee et al. show that a loss of adipose fatty acid oxidation (FAO) at thermoneutrality results in defective induction of thermogenic genes and mtDNA stress in BAT. Long-term housing of FAO-deficient mice results in a loss of interscapular BAT; however, body weight gain and glucose tolerance were unaffected.

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Loss of Adipose Fatty Acid Oxidation Does Not Potentiate Obesity at Thermoneutrality

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SUMMARY

Ambient temperature affects energy intake and expenditure to maintain homeostasis in a continuously fluctuating environment. Here, mice with an adipose-specific defect in fatty acid oxidation ($Cpt2^{A-/-}$) were subjected to varying temperatures to determine the role of adipose bioenergetics in environmental adaptation and body weight regulation. Microarray analysis of mice acclimatized to thermoneutrality revealed that $Cpt2^{A-/-}$ interscapular brown adipose tissue (BAT) failed to induce the expression of thermogenic genes such as *Ucp1* and *Pgc1α* in response to adrenergic stimulation, and increasing ambient temperature exacerbated these defects. Furthermore, thermoneutral housing induced mtDNA stress in $Cpt2^{A-/-}$ BAT and ultimately resulted in a loss of interscapular BAT. Although the loss of adipose fatty acid oxidation resulted in clear molecular, cellular, and physiologic deficits in BAT, body weight gain and glucose tolerance were similar in control and $Cpt2^{A-/-}$ mice in response to a high-fat diet, even when mice were housed at thermoneutrality.

INTRODUCTION

Obesity is driven by energy imbalance. Overconsumption of a calorie-dense diet increases energy storage mainly as triglyceride in white adipose tissue (WAT). Concomitantly, the inability to use this energy potentiates adiposity and body weight gain. Although great strides are being made in understanding the regulation of food intake, less is known about the regulation and contribution of energy expenditure to obesity. Determining the tissue-specific contribution of macronutrient metabolism to energy expenditure is critical for understanding the balance of energy intake and expenditure.

WAT plays an important role in energy storage but contains few mitochondria and contributes minimally to organismal bioenergetics in an autonomous manner. Alternatively, brown adipose tissue (BAT) is densely packed with mitochondria and can rapidly and robustly affect whole animal energy expenditure when deployed during a cold challenge (Harms and Seale, 2013). The physiological role of BAT is to produce heat to maintain body temperature during a cold challenge. This is accomplished via uncoupling cellular respiration from ATP generation via the mitochondrial transporter uncoupling protein-1 (Ucp1). Fatty acid oxidation is critical for this process (Guerra et al., 1998; Schuler et al., 2005; Tolwani et al., 2005) and provides the biophysical activator of uncoupling in BAT (Fedorenko et al., 2012). Mice with an adipose-specific loss of fatty acid oxidation are severely cold intolerant, demonstrating an autonomous requirement for adipose fatty acid oxidation in cold-induced thermogenesis (Ellis et al., 2010; Lee et al., 2015).

Because of the large potential to alter energy expenditure, it is tempting to suggest that defects in brown or beige adipocytes can lead to an obesogenic phenotype. Therefore, it was somewhat surprising that uncoupling protein-1 knockout (Ucp1KO) mice were resistant to rather than prone to diet-induced obesity (Enerbäck et al., 1997; Liu et al., 2003). One caveat is that standard laboratory animal housing is below the thermal preference for mice, generating a mild cold stress. Mice have a large surface-to-volume ratio and need to expend large amounts of energy defending their body temperature against the environment. Removing this cold stress by rearing mice at thermoneutrality (30°C) acutely reversed this phenotype and generated obesity-prone Ucp1KO mice, revealing a strong environmental impact on body weight and energy expenditure (Feldmann et al., 2009).

Recently, we generated mice with a loss of adipose fatty acid oxidation by knocking out carnitine palmitoyltransferase 2 (Cpt2), an obligate step in mitochondrial long-chain fatty acid β-oxidation (Lee et al., 2015). Similar to Ucp1KO mice, $Cpt2^{A-/-}$ mice were severely cold intolerant, but mildly resistant to high fat diet-induced adiposity. To understand the effect of ambient temperature on BAT deficient in fatty acid oxidation, we acclimatized $Cpt2^{A-/-}$ mice to thermoneutrality (30°C) and demonstrate a severe loss of agonist-induced thermogenic gene induction and loss of interscapular BAT after long-term housing of $Cpt2^{A-/-}$ mice at thermoneutrality. Surprisingly, given the severity of cold intolerance and suppression of molecular and cellular thermogenic programming in $Cpt2^{A-/-}$ BAT, thermoneutral housing did not affect diet-induced obesity in