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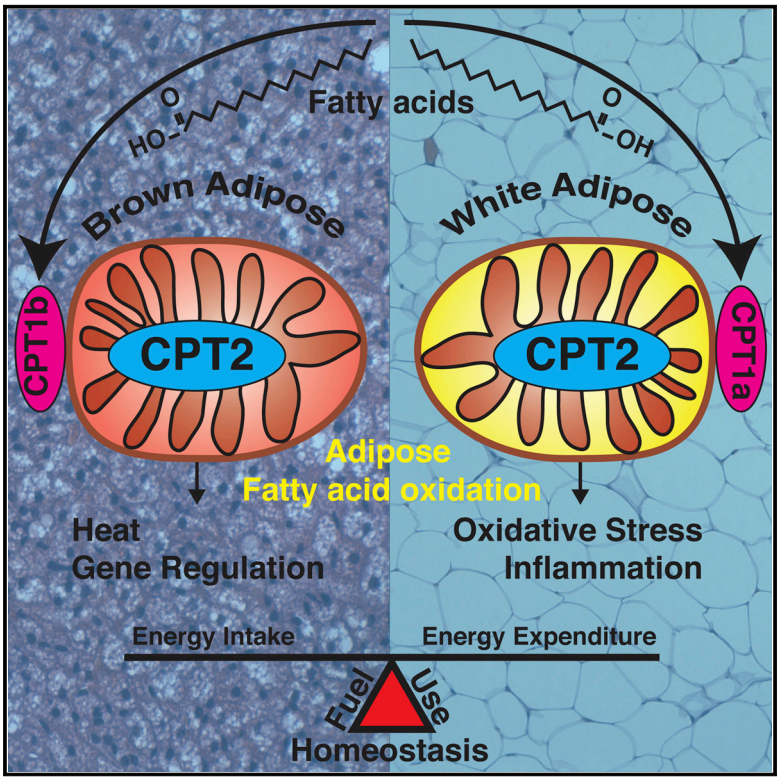
Adipose Fatty Acid Oxidation Is Required for Thermogenesis and Potentiates Oxidative Stress-Induced Inflammation

Graphical Abstract



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In Brief

In order to understand the contribution of adipose tissue fatty acid oxidation to whole-body energy homeostasis, Lee et al. deleted carnitine palmitoyltransferase 2 specifically in adipocytes. They show requirements for adipocyte fatty acid oxidation in cold-induced thermogenesis, gene expression in brown adipocytes, diet-induced adiposity, oxidative stress, and inflammation.

Highlights

- Adipose fatty acid oxidation (FAO) is required for cold-induced thermogenesis
- Adipose FAO is required for agonist-induced thermogenic gene expression
- Loss of adipose FAO does not alter body weight
- Adipose FAO is required for high-fat-induced oxidative stress and inflammation.

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Adipose Fatty Acid Oxidation Is Required for Thermogenesis and Potentiates Oxidative Stress-Induced Inflammation

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SUMMARY

To understand the contribution of adipose tissue fatty acid oxidation to whole-body metabolism, we generated mice with an adipose-specific knockout of carnitine palmitoyltransferase 2 ($CPT2^{A-/-}$), an obligate step in mitochondrial long-chain fatty acid oxidation. $CPT2^{A-/-}$ mice became hypothermic after an acute cold challenge, and $CPT2^{A-/-}$ brown adipose tissue (BAT) failed to upregulate thermogenic genes in response to agonist-induced stimulation. The adipose-specific loss of CPT2 resulted in diet-dependent changes in adiposity but did not result in changes in body weight on low- or high-fat diets. Additionally, $CPT2^{A-/-}$ mice had suppressed high-fat diet-induced oxidative stress and inflammation in visceral white adipose tissue (WAT); however, high-fat diet-induced glucose intolerance was not improved. These data show that fatty acid oxidation is required for cold-induced thermogenesis in BAT and high-fat diet-induced oxidative stress and inflammation in WAT.

INTRODUCTION

Ingestion of a calorically dense diet, generally high in fat content, coupled with inactivity leads to increased adiposity and eventual obesity. Obesity in turn is highly correlated with the development of type 2 diabetes, the metabolic syndrome, and cardiovascular disease, among others. The molecular mechanisms by which high-fat diets contribute to these pathologies are not well understood, but several themes have emerged. Implicated in the etiology and progression of obesity-related pathologies is oxidative stress, endoplasmic reticulum stress, and inflammation originating locally at adipose depots but acting systemically to promote insulin resistance (Glass and Olefsky, 2012; Hotamisligil, 2010; Keaney et al., 2003; Kusminski and Scherer, 2012). Reversing or preventing local adipose tissue inflammation may have beneficial systemic effects against insulin resistance. Alternatively, strategies to reverse obesity by increasing adipose energy expenditure have been suggested to improve systemic obesity-related complications (Tseng et al., 2010).

Adult mammals have at least two functionally distinct adipose lineages: unilocular white adipocytes, which function mainly to store fat, and multilocular brown adipocytes, which function mainly to burn fat for thermogenesis. Dysfunctional white adipose tissue (WAT) and brown adipose tissue (BAT) have been implicated in the pathogenesis of obesity and diabetes. BAT is densely packed with mitochondria and requires fatty acid oxidation to fuel heat generation (Ellis et al., 2010; Guerra et al., 1998; Ji et al., 2008; Schuler et al., 2005; Tolwani et al., 2005). Although the oxidation of fatty acids in WAT in the fed state is relatively low, fasting doubles the rate of white adipocyte fatty acid oxidation and is presumably a major fuel in insulin suppressed states (Wang et al., 2003). Changing macronutrient metabolism specifically in adipocytes can lead to changes in adiposity, body weight, and glucose tolerance (Abel et al., 2001; Ahmadian et al., 2011; Lodhi et al., 2012; Vernochet et al., 2012). However, the autonomous contribution of adipose fatty acid oxidation to obesity and insulin resistance remains unknown.

Mitochondrial long-chain fatty acid β-oxidation requires successive carnitine acyltransferases to translocate acyl-coenzyme As (acyl-CoAs) from the cytoplasm into the mitochondrial matrix (Wolfgang and Lane, 2006). The initial and rate-setting enzyme, CPT1, generates acylcarnitines that can traverse the mitochondrial membranes via specific transporters. CPT1 is allosterically inhibited by the rate-determining metabolite in de novo fatty acid synthesis, malonyl-CoA; therefore, the balance of fatty acid synthesis and oxidation is metabolically coordinated posttranslationally. Once inside the mitochondrial matrix, CPT2 generates acyl-CoAs from acylcarnitines to initiate the β-oxidation of long-chain fatty acids to acetyl-CoA. Fatty acids contain an abundant energy potential, making them ideal for storage during energy surplus and mobilization during energy deficits. Fatty acid oxidation efficiently generates energy but can also promote the generation of reactive oxygen species (ROS). ROS can potentiate oxidative stress and inflammation, which can impair insulin sensitivity (Houstis et al., 2006).

Although it is clear that fatty acid oxidation is a critical and fundamental metabolic endpoint in humans (Longo et al., 2006) and rodents (Ji et al., 2008; Nyman et al., 2005), it is not clear