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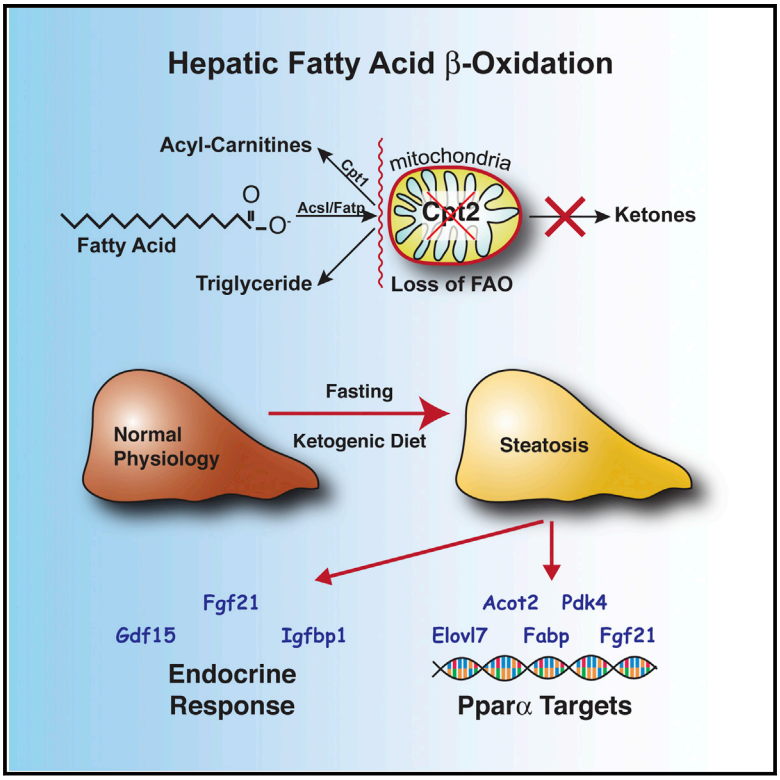
Cell Reports

Hepatic Fatty Acid Oxidation Restrains Systemic Catabolism during Starvation

Graphical Abstract



Highlights

- Hepatic fatty acid oxidation (FAO) is critical for liver physiology during starvation
- Hepatic FAO suppresses adipose lipolysis and systemic catabolism
- Upon fasting, loss of hepatic FAO induces Pparα target genes in the liver
- A ketogenic diet induces severe lipolysis and lethality in hepatic FAO-deficient mice

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In Brief

Lee et al. have generated mice that lack mitochondrial long-chain fatty acid β-oxidation specifically in the liver. They report that these mice can survive a 24-hr fast but not a low-carbohydrate ketogenic diet. Surprisingly, whole-body energy expenditure is largely maintained due to increased peripheral catabolism.

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Hepatic Fatty Acid Oxidation Restrains Systemic Catabolism during Starvation

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SUMMARY

The liver is critical for maintaining systemic energy balance during starvation. To understand the role of hepatic fatty acid β-oxidation on this process, we generated mice with a liver-specific knockout of carnitine palmitoyltransferase 2 ($Cpt2^{L-/-}$), an obligate step in mitochondrial long-chain fatty acid β-oxidation. Fasting induced hepatic steatosis and serum dyslipidemia with an absence of circulating ketones, while blood glucose remained normal. Systemic energy homeostasis was largely maintained in fasting $Cpt2^{L-/-}$ mice by adaptations in hepatic and systemic oxidative gene expression mediated in part by Pparα target genes including procatabolic hepatokines Fgf21, Gdf15, and Igfbp1. Feeding a ketogenic diet to $Cpt2^{L-/-}$ mice resulted in severe hepatomegaly, liver damage, and death with a complete absence of adipose triglyceride stores. These data show that hepatic fatty acid oxidation is not required for survival during acute food deprivation but essential for constraining adipocyte lipolysis and regulating systemic catabolism when glucose is limiting.

INTRODUCTION

Starvation initiates a series of metabolic adaptations to enable continuous production and delivery of nutrients to critical organs, tissues, and cells (Cahill, 2006). This response is coordinated in large part by the liver that responds by liberating glucose to the circulation initially from glycogen stores followed by de novo glucose production (i.e., gluconeogenesis). Additionally, ketones are produced and provide an alternative energy source to glucose for highly oxidative tissues such as the brain (Owen et al., 1967). Fatty acid oxidation is critical for these processes as it provides the carbon substrate for ketogenesis (acetyl-CoA) and mitochondrial bioenergetics (ATP, NADH) to facilitate gluconeogenesis. Therefore, humans with disparate inborn errors in mitochondrial fatty acid oxidation exhibit life-threatening hypoketotic-hypoglycemia following a fast (IJlst et al., 1998). Systemically, the liver produces most of the circulating ketones due to its high capacity for β-oxidation and lack of the CoA transferase (Oxct1) in hepatocytes that is required to utilize ketones (Cotter et al., 2011). Also, the liver is thought to dominate fasting gluconeogenesis with minor contributions from the kidney and gut. Interestingly, mice with a hepatocyte-specific loss of glucose-6-phosphatase, the obligate terminal enzyme in cellular glucose liberation, do not exhibit reduced blood glucose following fasting or starvation, although ketone production is accelerated (Mutel et al., 2011). Therefore, extra-hepatic gluconeogenic tissues can fully compensate for a loss of hepatic production.

Mitochondrial long-chain fatty acid β-oxidation is governed by the regulated translocation of activated fatty acids (acyl-CoAs) from the cytoplasm to the mitochondrial matrix mediated by successive carnitine acyltransferases (McGarry and Brown, 1997). Carnitine Palmitoyltransfersase 1 (Cpt1) isoenzymes mediate acyl transfer from long-chain acyl-CoAs to carnitine on the outer mitochondrial membrane, generating acylcarnitines that can traverse through the Carnitine-acylcarnitine translocase within the inner mitochondrial membrane. Within the mitochondrial matrix, Cpt2 transfers the acyl group from the acylcarnitine back onto CoA, enabling β-oxidation. Human inborn errors in Cpt2 result in increasing severity of metabolic disease (OMIM numbers, 255110 adult onset, 600649 infantile, and 600650 infantile lethal) (Isackson et al., 2008; Longo et al., 2006). The complete loss of *Cpt1a* or *Cpt1b* is embryonic lethal in mice, and the loss of *Acadl* or *Acadm* results in increased neonatal death (Ji et al., 2008; Kurtz et al., 1998; Nyman et al., 2005). The loss of other mitochondrial components of β-oxidation results in multisystemic defects as well as cell-specific compensatory mechanisms (Spiekerkoetter and Wood, 2010; Tolwani et al., 2005; Zhang et al., 2007, 2010).

To understand the contribution of hepatic fatty acid oxidation during fasting and starvation, we generated mice with a liver-specific knockout of Carnitine Palmitoyltransferase 2 ($Cpt2^{L-/-}$), an obligate enzyme in mitochondrial long-chain fatty acid β-oxidation encoded by a single gene. To our great surprise, $Cpt2^{L-/-}$ mice not only survived the perinatal period, but also did not exhibit alterations in blood glucose following a 24-hr fast although ketones were absent. Fasting resulted in serum dyslipidemia, hepatic steatosis, and alterations in hepatic and systemic oxidative gene expression. Although $Cpt2^{L-/-}$ mice were able to