Cutting fuel offers new clues in diabetic mystery

DOI 10.1074/jbc.H119.010075

P. Darrell Neufer

From the East Carolina Diabetes and Obesity Institute and Department of Physiology, Brody School of Medicine, East Carolina University, Greenville, North Carolina 27834

Edited by Jeffrey E. Pessen

Competing theories have held opposite views on the role of flux through β-oxidation in causing insulin resistance. New transcriptomics, proteomics, and metabolomics data of skeletal muscle from mice in which lipid oxidation is limited by restricting entry of fat into mitochondria reveal extensive remodeling of metabolic pathways, consistent with an overall reduction in metabolic efficiency and improved metabolic health. These findings point to a potential new therapeutic approach for treating insulin resistance and type 2 diabetes.

The term “insulin-resistant” emerged in the mid-1930s to describe diabetic patients who required more insulin than expected to lower blood glucose, a distinction that eventually led to the classification of type 2 diabetes (T2D). Insulin resistance (IR) reflects the gradual decrease in sensitivity of skeletal muscle, liver, and adipose tissue to insulin. It can persist for many (e.g. 10+) years before T2D develops, and it is typically associated with persistent nutrient overload, low levels of physical activity, and obesity. T2D is now one of the leading causes of mortality in adults worldwide, with the incidence in the United States currently 11% and projected to increase to as high as 33% of the adult population by the year 2050 (1). Given these forecasts, there is intense interest in identifying the primary molecular mechanism(s) responsible for the development of IR.

One mechanism that emerged in the early 2000s centered on the idea that proinflammatory lipids, such as fatty acyl-CoAs, diacylglycerols, and ceramides, accumulate in the cytosol when fatty acids cannot be catabolized via β-oxidation in the mitochondria, leading to activation of stress kinases that antagonize insulin-signaling proteins in skeletal muscle and liver. This mechanism gained rapid support after several studies found evidence of decreased skeletal muscle mitochondrial function (lower fatty acid oxidative capacity, mitochondrial number, resting metabolic flux, and ATP synthesis rates) in different types of patients with IR. This led to the prevailing theory that IR arises as a consequence of acquired or inherited mitochondrial dysfunction diverting fatty acids away from oxidation toward the production and cytosolic accumulation of proinflammatory lipids (2). The implication was that strategies to accelerate fatty acid oxidation would be protective against high-fat diet–induced IR, whereas inhibiting mitochondrial β-oxidation would promote IR.

More direct support for the theory came from studies involving acetyl-CoA carboxylase 2 mutant mice (Acc2−/−). ACC2 catalyzes the first step in fatty acid synthesis, producing malonyl-CoA, a potent allosteric inhibitor of carnitine palmitoyltransferase-1 (CPT1). CPT1 catalyzes the first step in the transport of fatty acids into mitochondria, and thus loss of ACC2 was predicted to lower malonyl-CoA levels, disinhibiting CPT1 and accelerating fatty acid oxidation. Acc2−/− mice were indeed characterized by elevated whole-body and muscle fatty acid oxidation rates as well as enhanced whole-body and muscle insulin sensitivity, even when maintained on a high-fat diet (3). The findings were consistent with the idea that accelerating fatty acid oxidation protects against high-fat diet–induced IR. However, subsequent studies using genetic and pharmacological strategies targeting β-oxidation, including additional whole-body and muscle-specific Acc2−/− knockout models (4, 5), failed to support these initial findings, generating confusion within the field.

To more directly test the relationship between skeletal muscle fatty acid oxidation and insulin sensitivity, Mynatt and colleagues (6) generated a mouse model with skeletal muscle-specific deletion of the muscle isoform of CPT1, CPT1b (CPT1bM−/−), thus limiting fatty acid entry into mitochondria and oxidation in skeletal muscle. Despite marked accumulation of intramuscular diacylglycerols and ceramide, indicating that lipid transport into the mitochondrial was indeed blocked, these mice exhibited improved whole-body glucose homeostasis. These data directly contradicted the mitochondrial dysfunction theory (2) while adding to a growing body of evidence suggesting that limiting, rather than accelerating, flux through mitochondrial β-oxidation protects against lipid-induced IR (7). However, the basis for this was unclear.

In the most recent study from this group, Ghosh et al. (8) used an integrated omics approach, combining transcriptomics, proteomics, and metabolomics, to more thoroughly characterize the adaptive responses in skeletal muscle of CPT1bM−/− mice. With mitochondria’s ability to take up fatty acids blocked, muscle predictably responds by invoking adaptations to enhance glucose, amino acid, and alternative lipid metabolism pathways (i.e. peroxisome biogenesis). Somewhat surprisingly, remodeling of amino acid catabolism and peroxisome biogenesis dominates the adaptive responses, presumably reflecting greater reliance on carbon flux through these pathways. The authors also observed that, despite evidence of ample
Figure 1. Model showing how the balance of mitochondrial lipid supply relative to demand regulates muscle insulin sensitivity. The left panel shows a normal cell in which the rate of ATP turnover (energy demand) matches the rate of fuel supply by virtue of mitochondria drawing the needed flux from catabolic pathways. The right panel depicts the consequence of fuel overload from fatty acids in the absence of any change in energy demand, thus increasing mitochondrial H$_2$O$_2$ emission, which is linked to the development of insulin resistance.

carbon (i.e. 14-fold higher acetyl-CoA levels) and reducing equivalent (NADH) supplies needed to support ATP synthesis, the adenosine energy charge was reduced, indicating that the mitochondrial respiratory system is unable to maintain as high a free energy of ATP (i.e. $\Delta G_{\text{ATP}}$) when fatty acid entry into mitochondria is restricted. Whether this reflects a difference in the efficiency of oxidative phosphorylation or other step in energy transfer is unknown. Furthermore, despite the diversion of lipids away from oxidation in skeletal muscle, CPT1b$^{-/-}$ mice on a chow diet (25% fat) gain body weight, fat free mass, and fat mass at a lower rate compared with controls (CPT1b$^{+/+}$). Daily activity and overall energy expenditure are slightly lower in CPT1b$^{-/-}$ mice, whereas food intake is similar initially but declines as the animals age. Interestingly, when the CPT1b$^{-/-}$ mice are weaned on, or switched, to a low-fat (10%) diet, their rate of weight gain and activity level are restored to those of controls (9), implying that the differences in body weight regulation in CPT1b$^{-/-}$ mice on a chow diet are linked to some other aspect of fat metabolism (e.g. increased peroxisomal oxidation). Collectively, the findings suggest that limiting fat entry into mitochondria diverts the flow of lipid-derived carbons through catabolic pathways that represent less efficient energy transformation processes. What accounts for this difference in efficiency awaits further study.

The study by Ghosh et al. (8) adds to a growing body of evidence supporting the concept that IR develops when mitochondrial fuel supply, particularly fatty acids, persistently outpaces energy demand (7) (Fig. 1). Mitochondria carry an enormous charge across the inner mitochondrial membrane ($\sim$300,000 V·cm$^{-1}$), a source of free energy that is converted to a chemical (ATP) charge and distributed throughout the cell. The mitochondrial respiratory system is therefore poised to continuously respond to the rate at which cellular energy charge is consumed (i.e. demand), drawing flux through catabolic pathways accordingly to supply the necessary reducing equivalents. An increase in the rate of fuel supply in the absence of demand therefore increases the reducing pressure in an already pressurized system, leading to the production of H$_2$O$_2$, altered redox homeostasis, and development of IR (10). Conversely, an increase in energy expenditure lowers the pressure in the system and is protective, even in the context of a high-fat diet. The initial Acc2$^{-/-}$ mouse model was likely protected against high-fat diet–induced IR not because flux through $\beta$-oxidation was increased in-and-of-itself, but because flux was increased by an unexplained increase in energy expenditure evident in this particular genetic model.

The study by Ghosh et al. (8) revealed extensive remodeling of metabolic pathways, changes that resemble adaptive responses to energy deficit and, as pointed out by the authors, are consistent with decreased predicted risk of a number of metabolically based diseases. Although promising, the potential health benefits are likely to be context-specific (i.e. chronic energy surplus) and dose-dependent and, as with any intervention, must account for the potential positive and negative impacts on bioenergetics. However, this study does add fuel to the argument that targeting CPT1b in muscle may be a viable therapeutic approach.

References

1. Boyle, J. P., Thompson, T. J., Gregg, E. W., Barker, L. E., and Williamson, D. F. (2010) Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. Popul. Health Metr. 8, 29 Medline

2. Lowell, B. B., and Shulman, G. I. (2005) Mitochondrial dysfunction and type 2 diabetes. Science 307, 384–387 CrossRef Medline

3. Abu-Elheiga, L., Oh, W., Kordari, P., and Wakil, S. J. (2003) Acetyl-CoA carboxylase 2 mutant mice are protected against obesity and diabetes induced by high-fat/high-carbohydrate diets. Proc. Natl. Acad. Sci. U.S.A. 100, 10207–10212 CrossRef Medline

4. Hoehn, K. L., Turner, N., Swarbrick, M. M., Wilks, D., Preston, E., Phua, Y., Joshi, H., Furler, S. M., Larance, M., Hegarty, B. D., Leslie, S. J., Pickford, R., Hoy, A. J., Kraegen, E. W., James, D. E., and Cooney, G. J. (2010) Acute or chronic upregulation of mitochondrial fatty acid oxidation has no net effect on whole-body energy expenditure or adiposity. Cell Metab. 11, 70–76 CrossRef Medline

5. Olson, D. P., Pulinilkunnil, T., Cline, G. W., Shulman, G. I., and Lowell, B. B. (2010) Gene knockout of Acc2 has little effect on body weight, fat mass, or food intake. Proc. Natl. Acad. Sci. U.S.A. 107, 7598–7603 CrossRef Medline

6. Wicks, S. E., Vandanmagsar, B., Haynie, K. R., Fuller, S. E., Warfel, J. D., Stephens, J. M., Wang, M., Han, X., Zhang, J., Noland, R. C., and Mynatt, R. L. (2015) Impaired mitochondrial fat oxidation induces adaptive remodeling of muscle metabolism. Proc. Natl. Acad. Sci. U.S.A. 112, E3300–E3309 CrossRef Medline

7. Muioo, D. M., and Neufert, P. D. (2012) Lipid-induced mitochondrial stress and insulin action in muscle. Cell Metab. 15, 595–605 CrossRef Medline

8. Ghosh, S., Wicks, S. E., Vandanmagsar, B., Mendoza, T. M., Bayless, D. S., Salbaum, J. M., Dearth, S. P., Campagna, S. R., Mynatt, R. L., and Noland, R. C. (2019) Extensive metabolic remodeling after limiting mitochondrial lipid burden is consistent with an improved metabolic health profile. J. Biol. Chem. 294, 12313–12327 CrossRef Medline

9. Warfel, J. D., Vandanmagsar, B., Wicks, S. E., Zhang, J., Noland, R. C., and Mynatt, R. L. (2017) A low fat diet ameliorates pathology but retains beneficial effects associated with CPT1b knockout in skeletal muscle. PLoS One 12, e0188850 CrossRef Medline

10. Fisher-Wellman, K. H., and Neufert, P. D. (2012) Linking mitochondrial bioenergetics to insulin resistance via redox biology. Trends Endocrinol. Metab. 23, 142–153 CrossRef Medline