Fatty Acid Oxidation and Insulin Action

When Less Is More

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Type 2 diabetes is a disease of metabolic dysregulation involving impaired uptake and utilization of glucose, altered lipid metabolism, accumulation of various lipid species in the circulation and in tissues, and disruption of metabolic signaling pathways that regulate insulin secretion from pancreatic islet β-cells. Normal fuel homeostasis involves reciprocal regulation of glucose and lipid catabolism. Fundamental contributions to our understanding of the interplay between these two key groups of metabolic fuels came from the work of Randle (1), who demonstrated that increased rates of fatty acid oxidation in the fasted state lead to suppression of glucose oxidation and activation of gluconeogenesis, thereby preserving blood glucose for use by the brain and central nervous system. Conversely, the transition from the fasted to the fed state involves a coordinated shift from fatty acid to glucose oxidation. A key element in the latter switch, as elegantly demonstrated by the work of McGarry (2), is the glucose-induced rise in malonyl CoA, which inhibits fatty acid oxidation via direct binding to and allosteric inhibition of carnitine palmitoyltransferase-1 (CPT-1), the rate limiting enzyme for transport of cytosolic long-chain acyl CoA molecules into the mitochondria for oxidation. The multifaceted roles of malonyl CoA as a key glucose-derived metabolite, an allosteric inhibitor of fatty acid oxidation, and a biosynthetic precursor for fatty acid synthesis has led to a series of recent studies investigating the effects of manipulating this metabolite in various tissues. A bonus of such experiments is the opportunity to assess the physiological impact of enhanced or diminished fat oxidation in different cell types and in whole animals. In this issue of *Diabetes*, one such study by Bouzraki et al. (3) demonstrates that high levels of malonyl CoA and reduced fat oxidation enhance glucose disposal in primary human skeletal myocytes.

Malonyl CoA is synthesized by carboxylation of acetyl CoA in a reaction carried out by either of the isoforms of acetyl CoA carboxylase (ACC), ACC-1 or ACC-2. ACC-1 is thought to reside in the cytosol and be primarily responsible for synthesis of the malonyl CoA pool involved in lipogenesis, whereas ACC-2 is thought to localize to the outer mitochondrial membrane, where malonyl CoA can be effectively used for allosteric regulation of CPT-1 (4). Malonyl CoA is decarboxylated to acetyl CoA by malonyl CoA decarboxylase (MCD), an enzyme that can be variously localized in the mitochondrial matrix, peroxisomes, or the cytosol (5). Both ACC and MCD activities are regulated by 5′AMP-activated protein kinase, which, when activated under conditions of energy deficit (e.g., fasting), phosphorylates ACC to reduce its activity while simultaneously phosphorylating MCD to increase its activity. The net effect is a rapid decrease in malonyl CoA levels, relief of CPT-1 inhibition, activation of fatty acid oxidation, and cessation of lipogenesis.

Bouzakri et al. studied the effects of inhibiting MCD activity in isolated human skeletal myocytes via transfection of the cultured cells with small interfering RNAs specific to the MCD transcript (3). They show that 75% inhibition of MCD expression with this method results in a doubling of malonyl CoA levels and a clear shift from fatty acid to glucose oxidation, in effect mimicking the fasted-to-fed transition. MCD inhibition also led to reduced palmitate uptake and decreased expression of fatty acid transport protein 1; conversely, glucose uptake in both the basal and insulin-stimulated states was enhanced in association with increased cell surface levels of GLUT4. Interestingly, although insulin-stimulated glucose uptake was increased in cells with suppressed MCD expression, no enhancement in insulin signaling was detected when measured at the levels of insulin receptor substrate-1 tyrosine phosphorylation, phosphatidylinoitol 3-kinase activity, or serine phosphorylation of Akt and glycogen synthase kinase-3. These results suggest that MCD suppression encourages glucose uptake and utilization through mechanisms that are independent of the known insulin signaling pathway. Based on these findings, the authors reasonably suggest that MCD may be a therapeutic target for patients with insulin resistance and type 2 diabetes.

Other recent studies provide direct insights into the potential and also the considerable complexities of developing MCD inhibitors for diabetes therapies. Thus, in one recent study, whole animal knockout of MCD conferred resistance to diet-induced impairment of insulin action, as shown by glucose tolerance testing (6). On the other hand, an earlier report found that overexpression rather than suppression of MCD in liver of rats fed on a high-fat diet ameliorated whole-animal, liver, and muscle insulin resistance (7). A unifying explanation for these seemingly discordant findings has recently been advanced (8). In this model, ingestion of diets high in fat and carbohydrate lead to accumulation of malonyl CoA in liver, resulting in hepatic steatosis and conversion of excess fats into species associated with hepatic insulin resistance such as diacylglycerol and ceramides. Consistent with this model,

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ACC, acetyl CoA carboxylase; CPT-1, carnitine palmitoyltransferase-1; MCD, malonyl CoA decarboxylase.

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overexpression of MCD in liver of high-fat–fed rats resolves hepatic steatosis and lowers circulating fatty acid levels while reversing insulin resistance (7).

In contrast, high-fat feeding actually increases rather than decreases β-oxidation in muscle due to transcriptional activation of the pathway and increased substrate supply (9). In sedentary animals, this induction appears to occur without a coordinated increase in tricarboxylic acid cycle flux, resulting in incomplete β-oxidation and accumulation of incompletely oxidized lipid intermediates that are thought to reflect mitochondrial stress (6,9). Knockout of MCD prevented incomplete fat oxidation in muscle and protected against diet-induced insulin resistance, suggesting a potential connection between mitochondrial overload and glucose intolerance (6). Surprisingly, lipid metabolism in the liver appeared to be relatively unaffected by this manipulation. Because MCD is present in three subcellular compartments, the tissue-specific consequences of its absence might reflect distinct distributions of the enzyme activity (5). In light of this possibility, it is important to emphasize that An et al. (7) overexpressed a form of the MCD gene that lacks the mitochondrial and peroxisomal targeting sequences, which, by design, resulted in liver-specific elevation of cytosolic activity. It is also noteworthy that the liver isoform of CPT-1 is 100-fold less sensitive to malonyl CoA than its counterpart in the muscle (1); this too could contribute to tissue-specific metabolic effects of MCD inhibition.

The foregoing findings in MCD-null mice appear to be consistent with those of Bouzakri et al. in human muscle cells in that they predict that knockdown of MCD in skeletal muscle, by raising malonyl CoA levels and inhibiting CPT-1, may prevent entry of long-chain acyl CoAs into the mitochondria, thereby making the mitochondrial oxidative machinery entirely available for glucose oxidation. Fitting with the notion that inhibition of muscle fat oxidation promotes glucose uptake, another recent report showed that genetic disruption of oxidative phosphorylation in mice produced an antidiabetic phenotype (10). In this study, a generalized, low-grade impairment of the electron transport chain was accomplished via targeted deletion of the mitochondrial flavoprotein apoptosis-inducing factor. Conditional knockout of apoptosis-inducing factor in mouse skeletal muscle not only increased glucose uptake and glycolytic metabolism, but also amplified insulin signaling when animals were fed either a low- or high-fat diet. Taken together, this new wave of evidence implies that insulin action in skeletal muscle couples directly to mitochondrial energetics and substrate selection, such that the internal GLUT4 pools are mobilized only when the muscle must rely on glucose as its primary source of fuel.

Still unanswered is the intriguing question of how the muscle cell senses a decline in the oxidation of fat and/or other fuels to engage an increase in glucose uptake and catabolism, especially when insulin signaling pathways are not enhanced. A clearer understanding of the metabolic and molecular signals that permit crosstalk between muscle mitochondria and GLUT4 trafficking now awaits future investigation. Also requiring further study is the impact of body-wide knockout or pharmacologic suppression of MCD, as this maneuver could exacerbate hepatic steatosis and compromise exercise tolerance and might also affect glucose oxidation and regulation of insulin secretion from pancreatic islets. Nonetheless, the emerging story on fat oxidation and insulin action in muscle suggests that perhaps less is better, at least in the context of inactivity and overnutrition.

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