Fatty acid oxidation in human skeletal muscle

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In this issue of the JCI, Rasmussen et al. (1) describe the functional regulation of fatty acid oxidation by hyperglycemia and hyperinsulinemia in human skeletal muscle. The authors report inhibition of long-chain fatty acid (LCFA) oxidation, but not medium-chain fatty acid (MCFA) oxidation, in association with increased intramyocellular malonyl-CoA concentrations. Normally, a glucose infusion designed to raise intramyocellular malonyl-CoA by creating hyperglycemia would suppress plasma FFA concentrations from the usual (∼500 µmol/l) to extremely low levels (<30 µmol/l) in normal, healthy volunteers, making measures of LCFA oxidation uninterpretable. By maintaining stable plasma FFA concentrations, the investigators could reasonably compare MCFA oxidation, a process not dependent upon carnitine palmitoyltransferase-1 (CPT-1), with LCFA oxidation, a process that is dependent upon CPT-1 activity. Malonyl-CoA is a potent inhibitor of CPT-1 activity (2), and thus increases in malonyl-CoA concentration should inhibit access of LCFAs into the mitochondria (Figure 1). These data are the best evidence to date that changes in intramyocellular malonyl-CoA participate in the regulation of LCFA oxidation in humans.

Intracellular fatty acid trafficking

As noted, insulin normally inhibits lipolysis (3), thereby lowering plasma FFA concentrations and depriving cells of the primary source of circulating lipid fuel. In addition, insulin drives glucose into cells, stimulating both glucose storage and oxidation. This increase in intracellular glucose metabolism leads to the synthesis of malonyl-CoA and generates increased amounts of glycerol-3-phosphate, a compound used by cells to esterify intracellular LCFA-CoA (but not MCFA) (Figure 1). Thus, hyperinsulinemia, such as that which normally occurs after meal ingestion, drastically limits the availability of FFA to muscle, further inhibits LCFA oxidation even if LCFAs enter the cell, and makes available more glycerol-3-phosphate for LCFA esterification into triglyceride.

The opposite situation occurs in circumstances such as starvation, where plasma insulin concentrations drop dramatically. Plasma FFA concentrations can increase dramatically (4) (3,000 µmol/l is not unheard of), and FFAs are readily taken up by muscle (5). The reduced uptake of glucose by muscle is thought to lower malonyl-CoA concentrations (2), permitting greater LCFA entry into the mitochondria.

Exercise also increases FFA uptake into muscle, but in this case there is also increased glucose uptake and oxidation. Under these circumstances, however, reduced activity of acetyl-CoA carboxylase-β (ACCβ) actually decreases malonyl-CoA concentrations, thus relieving any residual CPT-1 activity and increasing fatty acid oxidation.

One might question the utility of an intracellular regulator of LCFA entry into the mitochondria, given the 100-fold range of possible plasma FFA concentrations. Shouldn’t this range be more than sufficient to regulate muscle LCFA oxidation? It is clear, however, that intracellular events can magni-
The studies by Rasmussen et al. (1) have focused new attention on intracellular regulation of fatty acid oxidation. The strengths of this study are that it was performed in vivo in humans, and that fatty acid metabolism was measured in the leg, which is largely skeletal muscle. The measurement of both LCFA and MCFA oxidation is a sophisticated approach to address functional CPT-1 activity. The dramatic decrease in $^{13}$CO$_2$ release across the leg from $^{13}$C-labeled LCFA is good evidence for inhibition of LCFA oxidation by hyperinsulinemia and hyperglycemia. The lack of a decrease in $^{14}$CO$_2$ release from the leg from $^{14}$C-octanoate is reasonable evidence for ongoing MCFA oxidation.

**What remains to be learned**

There remain some unknowns despite the excellent study design and careful performance of this study. First, the hyperinsulinemia and hyperglycemia increase LCFA esterification independent of or dependent on an inhibition of LCFA oxidation? MCFAs cannot be esterified into triglycerides in humans and thus would not be diverted from oxidation pathways despite increased glycerol-3-phosphate. Could stimulation of imTG synthesis have been a primary effect? Because of the extreme difficulty of measuring leg respiratory quotient (RQ) (13), we also do not know whether leg fat oxidation was reduced during the hyperglycemia and hyperinsulinemia. Knowing whether leg fat was suppressed would be helpful because continued oxidation of LCFA-CoA from imTG sources might have diluted the $^{13}$C oxidation from plasma $^{13}$C-LCFA and could be detected by measurement of the leg RQ. Another obstacle is that uptake of MCFA across the leg is minimal (6–9%), making it difficult to accurately quantify; this, in turn, makes measurement of the regional oxidation difficult, because of the small arteriovenous differences in blood $^{14}$CO$_2$. Assuming that the values of leg MCFA oxidation are accurate, the leg accounted for only 3–5% of MCFA oxidation. It would also be helpful in future studies to determine the time course of inhibition of LCFA oxidation relative to malonyl-CoA changes. The present study reports changes in LCFA oxidation and a change in malonyl-CoA levels after 5 hours of significant hyperinsulinemia (insulin concentrations much higher than usually seen in type 2 diabetes) (13). Does LCFA oxidation decrease immediately, as one might expect it would? Does the increase in malonyl-CoA observed by these authors occur before the decrease in LCFA acid oxidation? Time-course experiments will help us decide whether the changes in malonyl-CoA concentration, with regard to LCFA oxidation, are likely of a cause-and-effect nature.

In summary, the intramyocellular regulation of CPT-1 by malonyl-CoA is a potent way to magnify (or blunt) the entry of LCFA into mitochondria in the face of dramatic shifts in FFA availability that occur in humans. One might question the need to further magnify 100-fold ranges in plasma FFA concentrations to which muscle cells are exposed. Exercise would seem to be the circumstance in which enhanced entry of LCFA into mitochondria is most desirable. Although FFA uptake increases with exercise, the need for LCFA for oxidation increases by well over 20-fold.

The potential role of imTG in providing LCFA to muscle mitochondria — and whether CPT-1 regulation by malonyl-CoA modulates this process — is an interesting and unexplored area. Given the importance of skeletal muscle in glucose disposal and the potential contribution of skeletal muscle to daily fat oxidation (in physically active humans), a further understanding of how skeletal muscle regulates LCFA oxidation may be helpful in saving us from the excess fat we seem to be accumulating.

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