JCI The Journal of Clinical Investigation

Fatty acid oxidation in human skeletal muscle

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J Clin Invest. 2002;110(11):1607-1609. https://doi.org/10.1172/JCI17303.

Commentary

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 […]

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J. Clin. Invest. **110**:1607–1609 (2002). doi:10.1172/JCI200217303.

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.

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Conflict of interest: The author has declared that no conflict of interest exists.

Nonstandard abbreviations used: long-chain fatty acid (LCFA); medium-chain fatty acid (MCFA); carnitine palmitoyltransferase-1 (CPT-1); acetyl-CoA carboxylase-β (ACC_β); intramyocellular triglyceride (imTG); respiratory quotient (RQ).

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 (ACC_β) 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-

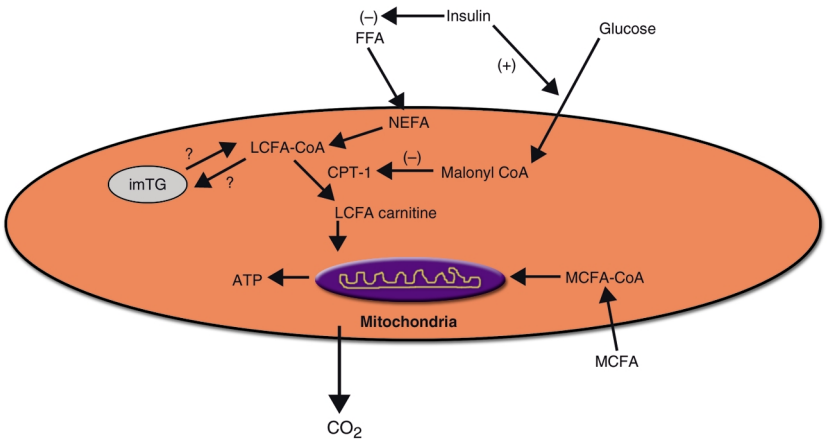

Figure 1

The major sites of regulation of fatty acid entry into myocellular mitochondria. Insulin inhibits (–) lipolysis, thus lowering FFA concentrations and limiting FFA availability for transport into muscle. Insulin stimulates (+) muscle glucose uptake, oxidation, and storage. Malonyl-CoA, generated as a result of insulin-stimulated glucose metabolism, inhibits CPT-1 and further reduces LCFA entry into the mitochondria. CPT-1 is not needed for MCFA to enter the mitochondria. The processes that regulate intramyocellular triglyceride synthesis and breakdown in humans are largely unknown.

fy (or counteract) the effects of these remarkable changes in the extracellular FFA on fuel oxidation. It is possible that intracellular LCFA-CoA concentrations are not entirely dependent upon extracellular concentrations, however. Rasmussen et al. (1) comment on the presence of intramyocellular triglycerides (imTGs) and how inhibition of LCFA oxidation by increased malonyl-CoA might stimulate imTG synthesis in the face of adequate extracellular FFA (6). It is known that these fatty acids are readily available during exercise (7), but it is possible that ongoing hydrolysis of imTG continues even when plasma FFA concentrations are markedly suppressed. Little is known about the regulation of imTG hydrolysis, and whether it might be a continued source of intracellular LCFA-CoA independent of the external FFA environment. If imTG hydrolysis continues despite insulin-mediated suppression of plasma FFA, the regulation of CPT-1 by malonyl-CoA (2) would safeguard muscle mitochondria from excess LCFA entry in the face of adequate glucose.

What is known about the regulation of imTG has been learned from the study of isolated muscle (8–10). Increased extracellular FFA (8) and insulin (9) stimulate imTG synthesis, whereas muscle contraction (8) and catecholamines (10) increase imTG hydrolysis. What the "background" rate of imTG hydrolysis might be and whether these same processes occur in human muscle are not known. At present, the functional role of imTGs remains unknown but potentially important given their association with insulin resistance (11).

The role of CPT-1 and its regulation by malonyl-CoA are especially of interest in the circumstances studied by Rasmussen et al. (1). The insulin-resistant/diabetic environment, with hyperglycemia and hyperinsulinemia, should result in increased malonyl-CoA and inhibition of LCFA-CoA entry into mitochondria. These LCFA-CoAs are then more available for imTG and diacylglycerol synthesis. Is it possible that under diabetic circumstances the imTG pools become sufficiently large that the LCFA generated by "basal" turnover of this pool overcomes the CPT-1 inhibition at the expense of high levels of intracellular LCFA-CoA? LCFA-CoA is thought to have adverse effects on insulin signaling (12).

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, did 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.

Acknowledgments

This work was supported by grants DK40484 and DK50456 from the US Public Health Service and by the Mayo Foundation.

1. Rasmussen, B.B., et al. 2002. Malonyl coenzyme A and the regulation of functional carnitine palmitoyltransferase-1 activity and fat oxidation in human skeletal muscle. *J. Clin. Invest.* **110**:1687–1693. doi:10.1172/JCI200215715.
2. Ruderman, N.B., Saha, A.K., Vavvas, D., and Witters, L.A. 1999. Malonyl-CoA, fuel sensing, and insulin resistance. *Am. J. Physiol. Endocrinol. Metab.* **276**:E1–E18.
3. Jensen, M.D., Caruso, M., Heiling, V., and Miles, J.M. 1989. Insulin regulation of lipolysis in nondiabetic and IDDM subjects. *Diabetes.* **38**:1595–1601.
4. Jensen, M.D., Haymond, M.W., Gerich, J.E., Cryer, P.E., and Miles, J.M. 1987. Lipolysis during fasting.

Decreased suppression by insulin and increased stimulation by epinephrine. *J. Clin. Invest.* **79**:207–213.
5. Jensen, M.D., Ekberg, K., and Landau, B.R. 2001. Lipid metabolism during fasting. 2001. *Am. J. Physiol. Endocrinol. Metab.* **281**:E789–E793.
6. Boden, G., Lebed, B., Schatz, M., Homko, C., and Lemieux, S. 2001. Effects of acute changes of plasma free fatty acids on intramyocellular fat content and insulin resistance in healthy subjects. *Diabetes.* **50**:1612–1617.
7. Guo, Z., Burguera, B., and Jensen, M.D. 2000. Kinetics of intramuscular triglyceride fatty acids in exercising humans. *J. Appl. Physiol.* **89**:2057–2064.
8. Spriet, L.L., Heigenhauser, G.J.F., and Jones, N.L. 1986. Endogenous triacylglycerol utilization by rat skeletal muscle during tetanic stimulation. *J. Appl. Physiol.* **60**:410–415.
9. Dyck, D.J., Steinberg, G., and Bonen, A. 2001. Insulin increases FA uptake and esterification but reduces lipid utilization in isolated contracting muscle. *Am. J. Physiol. Endocrinol. Metab.* **281**:E600–E607.
10. Peters, S.J., Dyck, D.J., Bonen, A., and Spriet, L.L. 1998. Effects of epinephrine on lipid metabolism in resting skeletal muscle. *Am. J. Physiol. Endocrinol. Metab.* **275**:E300–E309.
11. Pan, D.A., et al. 1997. Skeletal muscle triglyceride levels are inversely related to insulin action. *Diabetes.* **46**:983–988.
12. Dresner, A., et al. 1999. Effects of free fatty acids on glucose transport and IRS-1-associated phosphatidylinositol 3-kinase activity. *J. Clin. Invest.* **103**:253–259.
13. Kelley, D.E., and Mandarino, L.J. 1990. Hyperglycemia normalizes insulin-stimulated skeletal muscle glucose oxidation and storage in noninsulin-dependent diabetes mellitus. *J. Clin. Invest.* **86**:1999–2007.