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Improved Mitochondrial Function Is Linked With Improved Insulin Sensitivity Through Reductions in FFA

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Skeletal muscle insulin resistance (IR) is inextricably linked with the etiology of type 2 diabetes (T2D) and is a key target for prevention and treatment strategies. IR likely has many mechanistic origins, but the primary causes remain elusive, particularly in humans. Of the many possible mediators of IR, a considerable body of work has debated the potential roles of mitochondria (1–3), lipid oversupply (i.e., "lipotoxicity") (4,5), and the association between mitochondria, fatty acid metabolism, and intramyocellular lipid accumulation—the subject of this article. Indeed, substantial evidence exists to both support and refute a role for mitochondria in skeletal muscle insulin resistance (6,7).

In this issue, Daniele et al. (8) examined the associations among chronic free fatty acid (FFA) levels, intramyocellular lipids, the capacity for skeletal muscle mitochondrial ATP production and IR in human obesity and T2D. These investigators used a 2-week, single-arm, open-label acipimox treatment, which, consistent with this group's previous studies (9,10), significantly reduced circulating FFA levels and presumably availability to muscle and improved insulin sensitivity. The authors' central hypothesis was that chronic reduction in FFA would increase insulin sensitivity and that this would occur despite any change in the capacity for mitochondrial ATP production measured ex vivo in mitochondria isolated from muscle biopsy specimens. Their inherent argument was that this would rule out a role for mitochondria in FFA-induced IR.

Daniele et al. conducted a series of elegant ex vivo and in vivo studies in obese insulin-resistant subjects either with or without T2D. Contrary to their initial hypothesis, they found that reduction in elevated FFA in individuals with both T2D and normal glucose tolerance resulted in an increase in maximal carbohydrate and fatty acid–supported ATP production measured in mitochondria fractions isolated from vastus lateralis biopsy specimens. The reduction in FFA, however, did not decrease mitochondrial reactive oxygen species (ROS) measured as H_2O_2 emission from isolated mitochondrial fractions. Although no explicit hypothesis was stated, previous reports implicate mitochondria ROS in insulin resistance in high-fat diet–fed rodents and obese humans (1). These results are also apparently contradicted by a recent study by Phielix et al. (11), who reported that shorter-term acipimox treatment in patients with T2D did not increase mitochondrial respiration within intact myofibers and actually decreased maximal respiration in isolated mitochondria. Moreover, Phielix et al. (11) reported a decrease in mitochondrial H_2O_2 production with FFA reduction.

The ostensive inconsistency in the effects on mitochondria between these two studies can possibly be explained by the effects of FFA on mitochondrial uncoupling and/or efficiency. High FFA can cause mitochondrial uncoupling (12,13), and UCP3 has mild uncoupling properties and can help protect against FFA-induced oxidative stress (14). Thus, it is possible that reductions in FFA have disparate effects on mitochondrial O_2 consumption and ATP production, both of which could result in an increased coupling. It is also likely that the longer-term treatment in the study by Daniele et al. (8) had a fundamentally different effect on mitochondria. A deeper interrogation of mitochondrial respiratory states (e.g., basal, coupled and uncoupled respiration), in addition to ATP and H_2O_2 measurements, could have revealed these potentially important effects of FFA reduction.

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COMMENTARY

Measuring ATP production and H_2O_2 production in isolated mitochondria fractions has both advantages and drawbacks. On one hand, the measurements do not rely on measures of mitochondria content to interpret performance. However, this method requires a relatively large amount of biopsy specimen to isolate a sufficient amount of mitochondria. Moreover, the isolation procedure can result in a biased selectivity of the mitochondria analyzed (15).

Using high-resolution respirometry and fluorometric determination of H_2O_2 emission in small permeabilized myofiber bundles from muscle biopsy specimens could have alleviated this concern and would have permitted additional analyses in remaining tissue. For example, intramyocellular lipids could have been measured in vastus lateralis biopsies rather than relying on ^{1}H-magnetic resonance spectroscopy measures in a different muscle group (tibialis anterior), which can have much different fiber type and intramyocellular lipid content. As presented, the intramyocellular lipid data provide little useful information about the links among lipotoxicity, mitochondria, and IR.

As the role of intramyocellular lipids in IR is made more complicated by exercise (16), analyses of other potential lipid mediators of insulin action, such as ceramides or diacylglycerol, would have been informative. Further analyses of muscle metabolites could have also revealed effects of FFA reduction on lipid-mediated mitochondrial stress (2).

Daniele et al. (8) conclude that the mitochondrial defect in IR is partially reversible, which is consistent with other interventions, including weight loss and exercise, both of which also have profound effects on FFA metabolism and insulin sensitivity (17). However, this article used an intervention with specific direct FFA-lowering effects. These persuasive data support a link between FFA reduction and improved insulin sensitivity and mitochondrial ATP production. While not proving causality, this study makes an important contribution to our knowledge regarding the potential origins of IR; one that also has therapeutic implications. This study also helps to set the stage to further probe the complex functions of mitochondrial efficiency, coupling, and modulation of redox and oxidative stress and their respective role in fuel selection, including insulin resistance.

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Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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