Do the mitochondria of obese individuals respond to exercise training?

Obesity is associated with an increased risk for numerous disease states. The clustering of conditions in many obese patients, such as Type 2 diabetes, hypertension, dyslipidemia, and heart disease, known as the metabolic syndrome, is believed to be linked with the underlying insulin resistance commonly present with obesity (10). In terms of intervention, regularly performed, endurance-oriented physical activity is effective in enhancing insulin action in obese individuals and/or individuals with the metabolic syndrome (4). However, the cellular mechanisms by which endurance-oriented physical activity enhance insulin action in obese individuals are not clearly defined.

A potentially important alteration linked with the improvement in insulin action with endurance-oriented exercise training is an increase in mitochondrial density within the skeletal muscle fibers. An increased capacity for lipid oxidation via an exercise-induced increase in skeletal muscle mitochondrial content may decrease intramuscular lipid concentration, which could in turn enhance insulin signal transduction and ultimately improve insulin action (1, 9). This adaptation may be particularly critical in obese individuals where there is an increase in intramuscular lipid content that may induce insulin resistance (9). Also, a yet-undefined mechanism for improving insulin action may occur independently of intracellular lipid content, as an enhanced capacity for β-oxidation, similar to that seen with exercise training, improved insulin-mediated glucose transport without a corresponding decrease in intracellular lipid content (8). Together, such findings suggest that exercise-induced adaptations in the mitochondria may be an important factor explaining the improvement in insulin action evident with physical activity in obese individuals.

However, some data suggest that it may not be reasonable to automatically assume that obese individuals exhibit the classic proliferation in mitochondria, as commonly denoted by an increase in mitochondrial DNA (mtDNA), with endurance-oriented physical activity. A series of studies by several laboratories have indicated reductions in the activities of key regulatory enzymes involved in lipid transport, β-oxidation, and the Krebs cycle in sedentary, obese individuals (2, 6, 11, 12). In addition, mitochondrial structure and size are altered in a negative manner with obesity and Type 2 diabetes, with the skeletal muscle of obese individuals retaining plasticity; however, the nature of the adaptation to mild-intensity exercise training and weight loss intervention may differ from more typically observed mitochondrial adaptations reported in lean individuals performing vigorous physical activity. Specifically, the experiment designed by Menshikova et al. (7) set out to determine if the skeletal muscle mitochondria of obese individuals responded to a low-intensity, endurance-oriented exercise training and energy restriction intervention by increasing mitochondrial cristae and oxidative enzyme activities without corresponding mitochondrial proliferation as expressed by an increase in mtDNA. This experiment is relevant and timely in that it acknowledges that the mitochondria of obese individuals do differ from those in lean subjects, which may affect proliferative or other responses to exercise training and weight loss. A critical subtext is the clinical relevance of the findings, as the treatment examined (mild-intensity exercise coupled with dietary restriction) is a popular intervention in the treatment of obesity.

To test their hypothesis, Menshikova et al. (7) examined sedentary obese men and women before and after a 4-mo walking program that was coupled with dietary restriction to induce weight loss. The primary index of mitochondrial cristae proliferation was cardiolipin content; cardiolipin is an appropriate marker as it is a phospholipid present only in the inner mitochondrial membrane and also contributes to the integrity of the electron transport chain. mtDNA was used as the index of mitochondrial proliferation; other indexes of oxidative capacity such as citrate synthase (CS), succinate dehydrogenase (SDH), and electron transport chain (ETC) activities were also measured. As anticipated, the exercise training and weight loss intervention improved insulin action and maximal O₂ uptake (V₀₂ max); weight loss was ~9 kg. The most important finding relative to the hypothesis was that cardiolipin content significantly increased while mtDNA content was not altered. The magnitude of the increase in cardiolipin (+60%), indicative of an increase in mitochondrial cristae, was relatively similar to the increases in ETC enzyme activities (rotenone-sensitive NADH oxidase, +96%; ubiquinol oxidase, +48%) and larger than for CS (+29%) and SDH (+40%). The authors concluded that mild-intensity physical activity coupled with caloric restriction induced skeletal muscle mitochondrial biogenesis in the form of increased mitochondrial cristae but not mitochondrial proliferation. As pointed out by the authors, these data suggest that a different pattern of mitochondrial adaptation occurred, in contrast to other work where mtDNA and indexes of oxidative capacity such as CS increase proportionally with endurance-oriented physical activity (3). The nature of the mitochondrial biogenesis reported by Menshikova et al. (7) thus differs from the more classic adaptation to high-intensity aerobic activity in which mitochondrial amplification (increase in mtDNA) coupled with similar increases in oxidative enzyme activities along with increased mitochondrial size are the predominant features.

As with any quality scientific investigation, the work of Menshikova et al. (7) creates an opportunity for further studies.
Perhaps one of the more pressing issues would be dissecting out the individual effects of weight loss, obesity, and mild-intensity physical activity on mitochondrial plasticity. For example, an increase in mitochondrial cristae in the absence of a change in mtDNA may be an adaptation to exercise only when coupled with negative caloric balance; the negative caloric balance may, for example, counterbalance facets of mitochondrial proliferation. On the other hand, an increase in the surface area of the inner mitochondrial membrane without changes in mtDNA may be a response specific to either mild-intensity training or any physical activity performed by initially obese individuals. The relationship between the enhancement in mitochondrial cristae and insulin action also needs to be defined.

In conclusion, the study of Menshikova et al. (7) indicates that the nature of the mitochondrial adaptations evident with physical activity does differ. The main finding of this study (7) was that in obese individuals, mild-intensity physical activity with weight loss resulted in an increase in mitochondrial cristae (mitochondrial biogenesis) without changing mtDNA content (mitochondrial proliferation). The factors governing this alteration (i.e., obesity, exercise intensity, weight loss) remain to be discerned.

REFERENCES


Joseph A. Houmard
Human Performance Laboratory
Department of Exercise and Sport Science
East Carolina University
Greenville, North Carolina
e-mail: houmardj@ecu.edu