PGC-1α: important for exercise performance?

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SINCE THE IDENTIFICATION of the transcriptional coactivator peroxisome proliferator-activated receptor-γ coactivator (PGC)-1α as a factor interacting with PPARγ in brown adipose tissue (BAT) (12), it has become clear that PGC-1α plays important roles in regulating several cellular processes in many different tissues (10), including mitochondrial biogenesis in skeletal muscle (1, 9).

Previously, muscle-specific overexpression of PGC-1α resulted in the conversion of otherwise “white” glycolytic muscle to “red” oxidative muscle with a dramatic upregulation of typical oxidative genes/proteins like cytochrome c and cytochrome oxidase (9). These compelling findings indicated that simply overexpressing PGC-1α results in muscle characteristics usually found in highly endurance-trained muscle. It was in fact proposed that induction of PGC-1α might be used as “an exercise pill” providing the beneficial effects of exercise training without having to leave the couch (1a, 15). The importance of PGC-1α in regulating mitochondrial biogenesis in skeletal muscle has further been underlined by the reduced expression of genes/proteins involved in oxidative metabolism in skeletal muscle of both whole body and muscle-specific PGC-1α knockout mice (1, 4, 8). Moreover, the physiological impact of these modifications in skeletal muscle has consistently been reported by reduced exercise capacity of both whole body and muscle-specific PGC-1α knockout mice (4, 8).

In their article in the Journal of Applied Physiology, Calvo et al. (3) address the effects of increased muscle PGC-1α levels on exercise performance. Mice with muscle-specific overexpression of PGC-1α (MCK-PGC-1α) demonstrated marked improvements in exercise performance both during submaximal exercise intensities and during graded exercise to exhaustion. Intriguingly, the MCK-PGC-1α mice exhibited lower respiratory exchange ratio (RER) values during submaximal as well as maximal exercise intensities, reflecting that the molecular modifications induced by high PGC-1α levels increase fat oxidation and thus likely provide a carbohydrate-sparing effect relative to wild-type mice. Interestingly, at maximal exercise the RER value was below 1 in the MCK-PGC-1α mice, suggesting that no major metabolism/lactic acid-induced hyperventilation occurred.

The study by Calvo et al. (3) also presents mRNA data on genes encoding enzymes in oxidative metabolism, supporting previous findings (9), but also specifically increased mRNA levels of fat metabolism genes, suggesting an increased capacity for fat metabolism, which is supported by an increased fat oxidation during exercise in these mice.

The MCK PGC-1α mice also exhibited ~20% higher peak oxygen uptake than wild-type mice (3). This finding may seem surprising as the general opinion appears to be that whole body peak oxygen uptake at least in humans is limited by the pump capacity of the heart (13). However, despite possible species differences, the MCK-PGC-1α mice do have slightly elevated PGC-1α mRNA levels in the heart, and it may thus be speculated that this is sufficient to elicit the observed effects on peak oxygen uptake, although additional experiments are needed to clarify this. Of note, on the other hand, is also that very high levels of PGC-1α in the mouse heart will result in cardiomyopathy (7).

Together these findings show that PGC-1α-induced changes in metabolic protein expression profile can indeed change performance and metabolism during exercise in mice. This strongly supports that PGC-1α can be a key factor in regulating adaptive responses to regular endurance exercise, leading to enhanced oxidative capacity of skeletal muscle and thus increased capacity for both fat and carbohydrate utilization. As a single exercise bout elicits a transient increase in PGC-1α gene expression (2, 11) and AMPK has been shown to phosphorylate and activate PGC-1α (6), such exercise-induced regulation could be through both exercise-induced PGC-1α expression and AMPK-mediated PGC-1α activation (5). However, a previous study has suggested that skeletal muscle-specific PGC-1α overexpression can be associated with reduced exercise performance during high-intensity exercise, perhaps due to inability to utilize muscle glycogen (14), and PGC-1α knockout mice do in fact have the ability to increase the expression of mitochondrial proteins with training (8). Thus the actual physiological role of PGC-1α activation/expression in skeletal muscle in response to exercise still needs to be more carefully established.

REFERENCES


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