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Abstract

The peroxisome proliferator-activated receptor γ coactivator 1 (PGC-1) proteins are key regulators of cellular energy homeostasis in a number of oxidative tissues, including skeletal muscle. While the regulation and function of PGC-1α seems central to muscle fiber plasticity in endurance exercise, the role of PGC-1β in this tissue is less clear. Wright and coworkers now provide evidence for a protective effect of moderately elevated PGC-1β in electroporated rat skeletal muscle against high fat diet-induced insulin resistance at least in part by promoting the oxidation of long chain acyl-CoA entities and the elimination of reactive oxygen species. These data provide important insights into the biological role of PGC-1β in skeletal muscle and imply novel therapeutic avenues for improving peripheral insulin sensitivity.

Main text

Adequate oxidative capacity and mitochondrial function of skeletal muscle are crucial for maintaining systemic glucose and insulin levels and accordingly, the regulation of these processes is tightly controlled. In recent years, the three members of the peroxisome proliferator-activated receptor γ coactivator 1 (PGC-1) family of transcriptional coactivators have emerged as central regulators of energy homeostasis in muscle and other tissues. PGC-1α gene expression, protein levels and protein activity are affected by almost all of the signaling pathways that are activated in the contracting muscle fibers [1]. In turn, PGC-1α controls the adaptive changes elicited by endurance training [1]. In contrast to the more detailed informations about PGC-1α, much less is known about PGC-1β and the PGC-1-related coactivator (PRC). While the relative levels of physical activity is the dominant regulator of PGC-1α gene expression in skeletal muscle, transcriptional control of PGC-1β seems less coherent and different effects of exercise, denervation, dietary restriction, bariatric surgery, obesity or insulin stimulation on muscle PGC-1β transcript levels have been described, some with conflicting results in different experimental settings (summarized in refs. [1-4]). The elegant study by Wright and colleagues published in this issue of *Diabetologia* now sheds more light on the important role of PGC-1β in muscle physiology [2]. Wright *et al.* overexpressed PGC-1β in electroporated *tibialis cranialis* and *extensor digitorum longus* muscles of low fat- or high fat-fed rats. Despite the very moderate increase in PGC-1β levels, a significant elevation in mitochondrial oxidative capacity, reactive oxidative species detoxification and lipid metabolism ensued. Importantly though, ectopic expression of PGC-1β in the high fat-fed rats also boosted insulin sensitivity. While a causal link between reduced insulin resistance and the observed induction of long chain acyl-CoA metabolism and

antioxidant defense by PGC-1β was not examined, these long chain acyl-CoA and reactive oxygen species are strong candidate entities to contribute to the development of muscle insulin resistance [5].

A dysregulation of PGC-1α and PGC-1β gene expression levels has been found in skeletal muscle of prediabetic and type 2 diabetic individuals, at least in some populations [6, 7]. Studies in skeletal muscle-specific knockout mice for PGC-1α and PGC-1β alone failed to show a direct involvement of genetic ablation of the individual coactivators in the etiology of insulin resistance in this tissue [8-10]. The consequence of a PGC-1α/PGC-1β muscle-specific double knockout approach remains unknown. In contrast, the data provided by Wright and coworkers now suggest a protective role for PGC-1β against high fat diet-induced insulin resistance in skeletal muscle. Similarly, the moderate and acute modulation of electroporated PGC-1α in muscle resulted in improvement of insulin sensitivity in muscle of lean and obese Zucker rats [11]. Interestingly, the exact opposite observation, namely a more rapidly progressing insulin resistance, was observed in high fat-fed muscle-specific PGC-1α transgenic mice [12]. As in the study by Bonen and colleagues on PGC-1α [11], the electroporation-based approach to increase PGC-1β levels in individual muscles used by Wright and coworkers differs from the muscle-specific transgenic animals with a stronger, chronic elevation of PGC-1β [13]. For example, potentially confounding effects due to the strong transgenic expression, such as the strong inhibition of PGC-1α gene expression in the PGC-1β muscle-specific transgenic animals [13] that could contribute to the muscle fiber-type switch observed in these mice, were not encountered by Wright *et al*. Thus, in combination with the previous work by Bonen and colleagues [11], Wright et al. propose that a moderate, acute elevation of PGC-1α or PGC-1β, respectively, restores insulin sensitivity, at least in glycolytic muscles in rats. Accordingly, modulation of PGC-1α and PGC-1β gene expression might be an attractive novel therapeutic option against type 2 diabetes. However, pharmacological interventions aimed at the PGC-1 coactivators are not trivial to design [3]. First, chemical entities that selectively induce PGC-1α or PGC-1β gene expression in skeletal muscle remain elusive. Second, pharmacological methods that alter PGC-1 levels must hit a therapeutically beneficial window in order to avoid the detrimental effects associated with inadequate or excessive PGC-1 expression [3]. Finally, some paradoxical findings about the PGC-1 coactivators in muscle remain unexplained. For example, in the present study, PGC-1β expression and oxidative metabolism already increase as a consequence of the high fat diet and it is unclear how a further elevation of PGC-1β exerts the observed amelioration of insulin sensitivity. Moreover, while ectopic PGC-1β lowers the long chain acyl-CoA pool in muscle, the high fat diet-induced elevation of intramuscular ceramide and diacylglycerol, both strongly implicated in causing insulin resistance [5], is unaffected. It is also unclear how the chronic vs. acute and moderate vs. strong expression of PGC-1α and PGC-1β differ mechanistically and, at least in the case of PGC-1α, result in diametrically opposite outcomes in terms of peripheral insulin sensitivity. Whether this is also true for PGC-1β is unclear since the effect of the transgenic expression of PGC-1β in muscle on insulin resistance has not been elucidated yet [13]. Therefore, more studies are needed to fundamentally understand the regulation and function of the PGC-1s in skeletal muscle before an appropriate drug targeting strategy aimed at these coactivators can be attempted.

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Figure Legend

Figure 1. Overexpression of PGC-1β in glycolytic rat skeletal muscles improves insulin sensitivity. a, A high fat diet promotes the increase in intramuscular levels of ceramide, diacylglycerol (DAG), long-chain acyl CoA entities (LCACoA) and reactive oxygen species (ROS), all of which contribute to the development of insulin resistance. The reason for the increase in mitochondrial function and PGC-1β expression in muscle of high fat-fed rats remains unclear. It is conceivable that the resulting boost in fatty acid oxidation is an adaptive compensatory, yet inadequate mechanism to deal with the lipid overload. **b,** Ectopic expression of PGC-1β in

electroporated glycolytic rat muscles results in increased mitochondrial function, fatty acid metabolism and antioxidant defense. As a consequence, LCACoA levels are lowered. Despite the inability of ectopic PGC-1β to reduce intramuscular ceramide and DAG, an improvement in insulin sensitivity is achieved.

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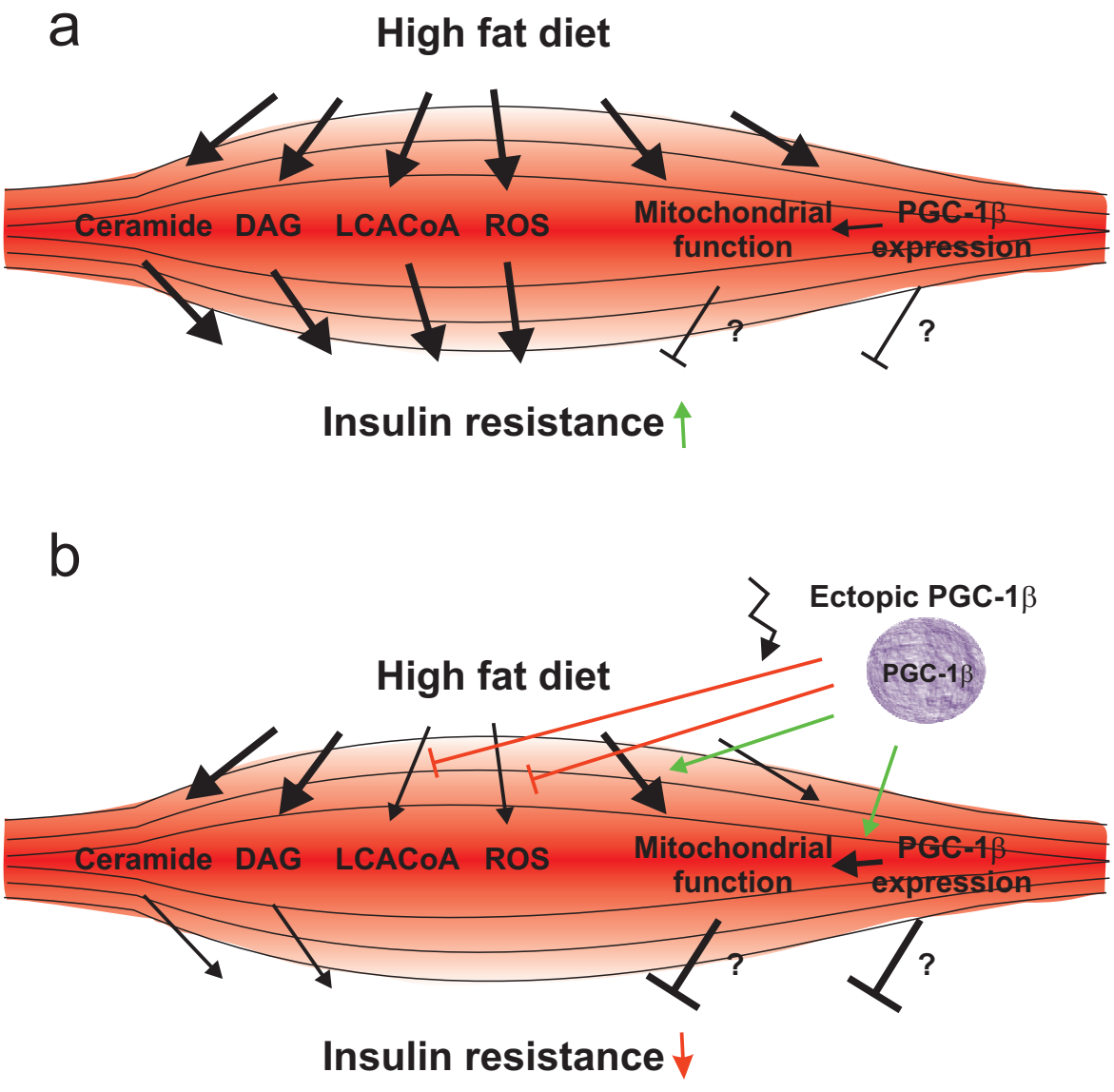
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