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Posted at edoc, University of Basel

Official URL: <http://edoc.unibas.ch/dok/A6043799>

Originally published as:

Summermatter, S. and Handschin, C.. (2012) *PGC-1 $\alpha$  and exercise in the control of body weight*. International journal of obesity and related metabolic disorders, Vol. 36, H. 11. S. 1428-1435.

# **PGC-1 $\alpha$ and exercise in the control of body weight**

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Published in Int J Obes (Lond). 2012 Nov;36(11):1428-35. PMID: 22290535. doi: 10.1038/ijo.2012.12

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## **PGC-1 $\alpha$ and exercise in the control of body weight**

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1 **Abstract**

2 The increasing prevalence of obesity and its comorbidities represents a major threat to human health  
3 globally. Pharmacological treatments exist to achieve weight loss, but the subsequent weight maintenance  
4 is prone to fail in the long run. Accordingly, efficient new strategies to persistently control body weight  
5 need to be elaborated. Exercise and dietary interventions constitute classical approaches to reduce and  
6 maintain body weight, yet people suffering from metabolic diseases are often unwilling or unable to move  
7 adequately. The administration of drugs that partially mimic exercise adaptation might circumvent this  
8 problem by easing and supporting physical activity. The thermogenic peroxisome proliferator-activated  
9 receptor  $\gamma$  coactivator 1 $\alpha$  (PGC-1 $\alpha$ ) largely mediates the adaptive response of skeletal muscle to endurance  
10 exercise and is a potential target for such interventions. Here, we review the role of PGC-1 $\alpha$  in mediating  
11 exercise adaptation, coordinating metabolic circuits and enhancing thermogenic capacity in skeletal  
12 muscle. We suggest a combination of elevated muscle PGC-1 $\alpha$  and exercise as a modified approach for  
13 the efficient long-term control of body weight and the treatment of the metabolic syndrome.

14

15 Key words: PGC-1 $\alpha$ , obesity, thermogenesis, energy expenditure, exercise, weight control

16

## 17 **Introduction**

18 Metabolic disorders are increasingly recognized as major threats to public health. Almost two thirds of the  
19 adult Americans are already overweight (body mass index  $>25 \text{ kg m}^{-2}$ ) and the prevalence will  
20 presumably rise in the future<sup>1</sup>. Projections indicate that 86.3% of the adult American population will be  
21 overweight and 51.1% will even have to be classified as obese (body mass index  $>30 \text{ kg m}^{-2}$ ) by the year  
22 2030<sup>2</sup>. Importantly, excessive body weight fosters the development of comorbidities such as hypertension,  
23 dyslipidemia, cancer, cardiovascular disease and diabetes<sup>3,4</sup> [ENREF 2](#).

24 A protracted energy imbalance where energy intake exceeds expenditure is considered as a key element in  
25 the etiology of metabolic impairments<sup>5,6</sup>. Reducing energy intake (by nutritional intervention), increasing  
26 energy expenditure (by physical activity) or the combination of both thus constitute cornerstones in the  
27 treatment of metabolic disorders<sup>7</sup>. Such lifestyle interventions generally lead to weight loss initially<sup>7</sup> and  
28 improve metabolic parameters<sup>8</sup>, but the majority of patients regain their weight in the long run<sup>9,10</sup>. A meta-  
29 analysis of studies published between 1931 and 1999 reveals a median success rate to maintain body  
30 weight after weight loss of a moderate 15%<sup>11</sup>. This impressive recidivism rate after otherwise successful  
31 weight loss is partially due to poor adherence to lifestyle interventions and potently facilitated by  
32 coordinate actions of ancestral physiological responses designed to powerfully defend and restore body  
33 energy stores<sup>12</sup>.

34 Indeed, weight loss initiated by reduced energy intake rapidly turns on a “thrifty” program which favors  
35 the eventual restoration of energy stores (Figure 1, outer circle)<sup>13</sup>. To this end, energy expenditure is  
36 suppressed in skeletal muscle, which is an important site of energy conservation during food restriction<sup>14</sup>.  
37 Concomitantly, adipose tissue increases its responsiveness towards the action of insulin<sup>15</sup>. Upon energy re-  
38 availability, energy is diverted from muscle to adipose tissue for accelerating fat mass replenishment<sup>13,15</sup>.  
39 <sup>16</sup> [ENREF 10](#). While such adaptive traits allowed the hunter-gatherers to deal with intermittent periods of  
40 famine and feast, and had thus survival value during human evolution, they nowadays strongly counteract  
41 any attempt to maintain body weight following successful weight loss<sup>17</sup>.

42 Similarly, the life of hunter-gatherers was characterized by alternating periods of high physical activity  
43 (hunting and searching for food) and rest (Figure 1, inner circle). Although these habitual physical  
44 activity-rest cycles have a shorter term (hours) compared with feast-famine cycles (days), the underlying  
45 mechanisms are reminiscent of those that operate during famine and feast<sup>18</sup>. During physical activity  
46 muscle energy stores like glycogen and triglycerides are depleted, but subsequently replenished in the  
47 resting phase. Such oscillations of muscle glycogen and triglyceride levels with physical activity-rest  
48 cycles during tens of thousands of years resulted in the selection of a “thrifty” program with a high  
49 proficiency to restore muscle energy stores. A decreased turn-over in muscle glycogen and  
50 intramyocellular lipids (IMCLs) is postulated to ultimately impair skeletal muscle insulin sensitivity<sup>18</sup>.  
51 <sup>19</sup> [ENREF 17](#).

52 A successful long-term body weight control, with concomitant prevention of metabolic derangements,  
53 consequently has to fulfill two requirements: a) avoidance of energy conservation in muscle tissue  
54 following weight loss in order to prevent obesity relapse and b) regular metabolic cycling in skeletal  
55 muscle in order to prevent excessive accumulation of glycogen and lipids.

56 Intriguingly, life-long regular exercise would meet both demands (Figure 1), but the long-term adherence  
57 is prone to failure. Exercise pills that mimic the plastic adaptations to exercise would be an alternative  
58 treatment of choice, but the high complexity of exercise hampers the unraveling and pinpointing of a  
59 single pathway that mimics all effects of exercise<sup>20, 21</sup> [ENREF 19](#). Nonetheless, targeting key mediators of  
60 physical activity in skeletal muscle constitutes a promising approach to support, facilitate and/or amplify  
61 the effects of exercise in manipulating energy expenditure, promoting metabolic cycling and thus finally  
62 controlling body weight and promoting metabolic health. In the following section, we will outline why the  
63 peroxisome proliferator-activated receptor  $\gamma$  coactivator 1 $\alpha$  (PGC-1 $\alpha$ ) represents an excellent target and  
64 summarize the central role of PGC-1 $\alpha$  in mediating exercise adaptation, coordinating metabolic circuits  
65 and enhancing thermogenic capacity in skeletal muscle.

66 **PGC-1 $\alpha$  is a central, integrative hub in exercise adaptation**

67

68 ***Physiological induction of PGC-1 $\alpha$  by exercise***

69 Muscle contraction activates a myriad of signaling cascades and many of those ultimately converge on  
70 PGC-1 $\alpha$  to increase its expression levels and activity<sup>22</sup>. The AMP-dependent kinase (AMPK) and the  
71 mitogen-activated protein kinase (MAPK) p38 are both activated in response to contraction<sup>23,24</sup> and  
72 subsequently phosphorylate the PGC-1 $\alpha$  protein<sup>25</sup>. Exercise also leads to de-acetylation and activation of  
73 PGC-1 $\alpha$ . Different mechanisms regulating the acetylation level of PGC-1 $\alpha$  have been proposed involving  
74 direct de-acetylation of PGC-1 $\alpha$  by SIRT1 (silent mating type information regulator 2 homolog 1)<sup>26,27</sup> or  
75 inhibition of acetylation by exclusion of the acetyltransferase GCN5 from the nucleus<sup>28</sup>.

76 Transcription of PGC-1 $\alpha$  is regulated by the motor-neuron-induced rise in intracellular calcium, which  
77 leads to activation of calcium/calmodulin dependent protein kinases (CaMKs) and of the protein  
78 phosphatase calcineurin A (CnA)<sup>25,29</sup>. Subsequently, the altered phosphorylation status of MEF2C/D and  
79 the cyclic AMP-responsive element binding protein (CREB) result in an activation of these transcription  
80 factors, binding to the PGC-1 $\alpha$  promoter and induction of PGC-1 $\alpha$  transcription. In addition, exercise-  
81 induced activation of AMPK, p38,  $\beta_2$ -adrenoceptor signaling, reactive oxygen and nitrogen species  
82 promote the transcription of PGC-1 $\alpha$ <sup>30,31</sup>. Three different splice variants of PGC-1 $\alpha$  (PGC-1 $\alpha$ -a, PGC-1 $\alpha$ -  
83 b and PGC-1 $\alpha$ -c) are induced by exercise<sup>32</sup>. Compared with PGC-1 $\alpha$ -a mRNA, PGC-1 $\alpha$ -b or PGC-1 $\alpha$ -c  
84 mRNAs are transcribed from a different exon 1<sup>32</sup>. In mice, activation of AMPK increases the levels of all  
85 three PGC-1 $\alpha$  isoforms, while  $\beta_2$ -adrenoceptor signaling acts on the expression of PGC-1 $\alpha$ -b and PGC-1 $\alpha$ -  
86 c<sup>32</sup>. Similarly, in human muscle PGC-1 $\alpha$ -a and PGC-1 $\alpha$ -b are both activated by AMPK, while  $\beta_2$ -  
87 adrenoceptor signaling seems to act mainly on PGC-1 $\alpha$ -b<sup>33</sup>. Effects of other exercise-induced stimuli on  
88 the expression of different isoforms have not been examined to date. After bouts of endurance exercise,  
89 the total PGC-1 $\alpha$  levels and its activity in skeletal muscle are consequently elevated. An auto-regulatory  
90 loop exists where PGC-1 $\alpha$  further increases its own expression<sup>29</sup>. Once transcribed and activated PGC-1 $\alpha$   
91 carries out its various functions as summarized below.

92 ***PGC-1 $\alpha$  in fiber type switching***

93 Type I and IIa slow-twitch, high-endurance muscle fibers express high levels of PGC-1 $\alpha$ , which largely  
94 determine the fiber-type composition of skeletal muscle. Ectopic expression of PGC-1 $\alpha$  in skeletal muscle  
95 *per se* is sufficient to promote fiber-type switching<sup>34</sup>. Indeed, overexpression of PGC-1 $\alpha$  shifts muscle  
96 appearance from a white to a reddish color<sup>34</sup>, promotes mitochondrial biogenesis of intramyofibrillar and  
97 subsarcolemmal mitochondria with concomitant reductions in myofibrillar volume<sup>35</sup>, alters myosin heavy  
98 chain (MHC) composition from MHC IIb and x towards more IIa and I<sup>34</sup>, switches metabolism from  
99 glycolytic to oxidative<sup>34</sup> and slows down calcium handling<sup>35</sup>. Consequently, endurance performance is  
100 improved, while maximal force generation is significantly reduced<sup>35</sup>. Inversely, PGC-1 $\alpha$  muscle-specific  
101 knock-out animals exhibit a shift from oxidative type I and IIa towards type IIx and IIb muscle fibers, and  
102 a reduced oxidative capacity<sup>36, 37</sup>. Thus, PGC-1 $\alpha$  seems to drive fiber-type conversion in all its facets.

103 ***PGC-1 $\alpha$  in angiogenesis***

104 PGC-1 $\alpha$  regulates the angiogenic vascular endothelial growth factor (VEGF). This induction of VEGF by  
105 PGC-1 $\alpha$  is independent of the canonical hypoxia response pathway and hypoxia inducible factor (HIF).  
106 Instead, PGC-1 $\alpha$  co-activates the orphan nuclear receptor ERR $\alpha$  (estrogen-related receptor  $\alpha$ , NR3B1) on  
107 conserved binding sites found in the promoter and in a cluster within the first intron of the VEGF gene<sup>38</sup>.  
108 Consequently, PGC-1 $\alpha$  promotes vascularization of skeletal muscle and thereby supports oxygen and  
109 nutrient supply.

110 ***PGC-1 $\alpha$  and myokines***

111 Skeletal muscle emerged furthermore as an endocrine organ, which releases myokines (cytokines from  
112 muscle) in response to exercise<sup>39</sup>. Given that PGC-1 $\alpha$  mediates the effects of exercise to a high extent, the  
113 question arose, whether PGC-1 $\alpha$  is involved in myokine production and release. Loss-of-function studies  
114 of PGC-1 $\alpha$  gene expression in murine skeletal muscle revealed a systemic, low-grade, chronic  
115 inflammation characterized by elevated circulating levels of interleukin 6 (IL-6) and tumor necrosis factor



116  $\alpha$  (TNF $\alpha$ )<sup>36,37</sup>. It remains currently unresolved, whether ectopic expression of PGC-1 $\alpha$ , in turn, diminishes  
117 the production and release of these cytokines.

### 118 *PGC-1 $\alpha$ in coordinating muscle metabolism and enhancing metabolic flexibility*

119 In respect to metabolism, PGC-1 $\alpha$  exerts very versatile effects on skeletal muscle. It coordinately  
120 increases the expression of key regulators of lipid oxidation (MCAD; Medium Chain Acyl CoA  
121 Dehydrogenase, CPT1b; Carnitine palmitoyltransferase), Krebs cycle (Citrate synthase) and oxidative  
122 phosphorylation (Subunits of complexes I to IV)<sup>40</sup>.

123 However, a careful regulation of this process is important since excessive or dysbalanced oxidative  
124 metabolism impairs insulin sensitivity. Acylcarnitines are generated when the amount of lipids fluxed into  
125  $\beta$ -oxidation exceeds the capacity of the Krebs cycle and/or oxidative phosphorylation (OXPHOS)<sup>41</sup>. These  
126 detrimental lipid species are subsequently released into the circulation and contribute to the development  
127 of insulin resistance<sup>41-43</sup>. Similarly, the proton gradient that generates the mitochondrial membrane  
128 potential is a potential source of reactive oxygen species (ROS), which are also implicated in the etiology  
129 of insulin resistance<sup>44</sup>.

130 Intriguingly, PGC-1 $\alpha$  restrains these processes from excessive activation by concomitantly boosting the  
131 expression of negative regulators of lipid catabolism. The levels of inhibitors of lipid oxidation (ACC2),  
132 antagonists of ROS generation (UCP3; Uncoupling Protein and ANT; Adenine Nucleotide Translocator),  
133 and ROS-detoxifying enzymes are all elevated by PGC-1 $\alpha$ <sup>40,45</sup>. While the overall gene expression pattern  
134 is ambiguous, the net rates are nonetheless clearly showing an increased oxidation of fatty acids and an  
135 elevated mitochondrial membrane potential<sup>40</sup>. Therefore, the increased  $\beta$ -oxidation and the subsequent  
136 Krebs cycle and OXPHOS are tightly regulated and balanced by PGC-1 $\alpha$ . The concomitant induction of  
137 both positive and negative regulators of fatty acid oxidation and OXPHOS through PGC-1 $\alpha$  boosts  
138 metabolic flexibility and restrains excessive oxidation<sup>40</sup>.

139 In addition, PGC-1 $\alpha$  drives glucose uptake and determines fuel selection<sup>46</sup>. Glucose is diverted away from  
140 glycolysis and oxidation by inhibiting the activity of the pyruvate dehydrogenase complex through PDK4

141 (pyruvate dehydrogenase kinase 4)<sup>47, 48</sup> [ENREF 44](#). This is further substantiated by the reduced lactate  
142 production and glucose oxidation rates following overexpression of PGC-1 $\alpha$ <sup>47</sup>. Rather glucose is used to  
143 replenish glycogen stores or shunted towards the pentose phosphate pathway to serve as substrate for *de-*  
144 *novo* lipogenesis<sup>46, 47</sup>. Indeed, PGC-1 $\alpha$  regulates the expression of the fatty acid synthase promoter through  
145 its interaction with liver x receptor  $\alpha$  (LXR $\alpha$ , NR1H3)<sup>46</sup>. Furthermore, PGC-1 $\alpha$  drives the expression of  
146 genes involved in lipid esterification into triglycerides<sup>46, 49</sup> [ENREF 39](#). Subsequently, intramyocellular  
147 lipids accumulate. PGC-1 $\alpha$  is therefore a metabolic master regulator that induces and controls catabolic  
148 and anabolic pathways in skeletal muscle.

#### 149 ***Is there a role for muscle PGC-1 $\alpha$ in energy expenditure?***

150 Total energy expenditure consists of various components. Principally, there are three major components of  
151 energy expenditure: basal metabolic rate (BMR), diet-induced thermogenesis (DIT) and activity  
152 thermogenesis (AT)<sup>50</sup>. BMR is the energy expended when an individual is lying at complete rest, in the  
153 morning, after sleep, in the postabsorptive state. In individuals with sedentary occupations BMR accounts  
154 for approximately 60% of total daily energy expenditure. DIT is the energy expenditure associated with  
155 the digestion, absorption, and storage of food and accounts for approximately 10–15% of total daily  
156 energy expenditure. AT has to be further separated into two sub-components: non-exercise activity  
157 thermogenesis (NEAT)<sup>51</sup> (including fidgeting, muscle tone and posture maintenance, and other low-level  
158 physical activities of everyday life<sup>52</sup>) and exercise-related activity thermogenesis (ERAT). In the  
159 following we will mainly refer to energy expenditure in the sedentary state (i.e. the total of BMR, DIT and  
160 NEAT), and energy expenditure in response to exercise (ERAT).

161 Skeletal muscle comprises 40% of body weight and, in the absence of physical activity, accounts for 20-  
162 30% of energy expenditure<sup>53</sup>. The possibility arises that by altering skeletal muscle function, PGC-1 $\alpha$   
163 might increase energy expenditure in the sedentary state. Indeed adenoviral over-expression of PGC-1 $\alpha$  in  
164 muscle cells *in vitro* elevates oxygen consumption and proton leak<sup>54, 55</sup> [ENREF 22](#). Consistently,  
165 physiological overexpression of PGC-1 $\alpha$  increases oxygen consumption in isolated mitochondria<sup>56</sup>. In

166 mice with ectopic expression of PGC-1 $\alpha$  in skeletal muscle, energy expenditure is, however, not  
167 elevated<sup>49,57</sup> [ENREF 46](#), indicating that the increase in muscle oxygen consumption is possibly too  
168 moderate to influence whole body energy expenditure, not detectable or compensated. Thus an effect of  
169 PGC-1 $\alpha$  on energy expenditure in the sedentary state -although likely- could so far not conclusively been  
170 demonstrated *in vivo*.

171 Originally, PGC-1 $\alpha$  was discovered as a mediator of adaptive thermogenesis in both brown fat and  
172 skeletal muscle of mice upon cold exposure<sup>58</sup>. The underlying mechanism in brown adipose tissue rapidly  
173 emerged. Brown adipose tissue is innervated by the sympathetic nervous system (SNS) and upon cold  
174 exposure, SNS nerve endings in BAT release noradrenaline, which activates  $\beta$ -adrenergic receptors. The  
175 subsequent induction of PGC-1 $\alpha$  increases expression and activation of the uncoupling protein 1 (UCP1),  
176 dissipation of the electron gradient and an increase in oxygen consumption<sup>58,59</sup> [ENREF 52](#). For a long  
177 time, similar mechanisms were believed to act in skeletal muscle and the discovery of the UCP1  
178 homologue UCP3 in muscle has further spurred this idea. In the meantime, conflicting results pertaining to  
179 the role of UCP3 as an uncoupler have been reported and interest has waned<sup>60-63</sup> [ENREF 52](#).

180 The molecular mechanisms that mediate adaptive thermogenesis in skeletal muscle remain obscure. A  
181 model has been proposed implicating futile substrate cycling between lipid oxidation and *de-novo*  
182 lipogenesis in response to hormonal stimulation<sup>64,65</sup>. Given that PGC-1 $\alpha$  concomitantly promotes lipid  
183 oxidation and lipogenesis the possibility arises that PGC-1 $\alpha$  has the potential to modulate oxygen  
184 consumption via substrate cycling upon adequate stimulation (e.g. exercise). During acute exercise, the  
185 PGC-1 $\alpha$ -supported catabolism will prevail, leading to ATP generation for muscle contraction, while PGC-  
186 1 $\alpha$ -supported anabolism will further consume ATP post exercise. This temporal dissociation might allow  
187 optimal energy utilization during acute exercise and concomitantly energy dissipation during entire  
188 activity-rest cycles.

189 ERAT constitutes the component of energy expenditure that can volitionally be modified by increasing the  
190 level of muscle work. Upon physical activity, skeletal muscle metabolism changes dramatically and

191 muscle oxygen consumption can account for up to 90% of the whole body oxygen uptake during this  
192 period<sup>53</sup>. Exercise depletes ATP, glycogen and IMCL stores and complements the action of PGC-1 $\alpha$ ,  
193 which, besides promoting oxidative metabolism, drives the refueling of energy stores. These concerted  
194 processes result in a high turnover of metabolic cycling and are thermogenic (Figure 2). In response to  
195 exercise, the respiratory exchange rate (RER) (ratio VCO<sub>2</sub>/VO<sub>2</sub>) is diminished and the peak oxygen  
196 consumption elevated in PGC-1 $\alpha$  transgenic compared to wild-type animals<sup>57</sup>.

197 Taken together, muscle PGC-1 $\alpha$  in the absence of stimulation (cold exposure or exercise), seems not to  
198 affect whole body energy expenditure.

### 199 **Muscle PGC-1 $\alpha$ in the regulation of whole body glucose homeostasis**

200 By modulating skeletal muscle function, PGC-1 $\alpha$  plays an important role in regulating whole body  
201 glucose homeostasis. Indeed, muscle PGC-1 $\alpha$  and overall metabolism seem to be highly interrelated.  
202 Abnormally low PGC-1 $\alpha$  levels have been described in the skeletal muscle of type 2 diabetic patients and  
203 physically inactive individuals<sup>66, 67</sup>. Direct evidence for a role of muscle PGC-1 $\alpha$  in controlling whole  
204 body glucose homeostasis derives from studies in mice where reduced or ablated expression of the gene  
205 encoding PGC-1 $\alpha$  results in abnormal systemic glucose and insulin homeostasis<sup>36, 37</sup>. Inversely, transgenic  
206 mice with elevated muscle PGC-1 $\alpha$  levels do not display improved whole body glucose homeostasis in the  
207 sedentary state, and even develop peripheral insulin resistance on a high-fat-containing diet, possibly due  
208 to increased lipid accumulation in skeletal muscle<sup>40, 49, 57</sup> [ENREF 15](#).

### 209 **Exercise is the real thing: PGC-1 $\alpha$ - a partial exercise mimetic, not a substitute**

210 Exercise induces a complex pleiotropic response in skeletal muscle. Even one single bout of endurance  
211 exercise comprises changes in the expression of more than 900 genes<sup>68</sup>. To a considerably high extent  
212 PGC-1 $\alpha$  mimics the effects of exercise, yet PGC-1 $\alpha$  induction is not a replacement for exercise. In the  
213 following section we will highlight the most prominent differences between exercise as a physiological  
214 stimulus of muscle contraction and muscle-specific over-expression of PGC-1 $\alpha$  as an “exercise mimetic”.

215

216 Intriguingly, ectopic expression of PGC-1 $\alpha$  can exert positive feedback on some of its alleged upstream  
217 activators. The neuromuscular junction program is regulated by PGC-1 $\alpha$ <sup>69</sup>. Furthermore, the activity of  
218 calcium-dependent signaling pathways via prolongation of myoplasmic calcium transients is increased by  
219 PGC-1 $\alpha$  and similarly PGC-1 $\alpha$  activates the transcription of nitric oxide synthase (inducible and  
220 endothelial, but not neuronal), which promotes elevated levels of nitric oxide<sup>35, 70</sup>. By contrast, some other  
221 upstream activators, namely AMPK and p38 are not affected by ectopic expression of PGC-1 $\alpha$ <sup>49, 71</sup>. On the  
222 contrary, glycogen levels are elevated in response to PGC-1 $\alpha$  and an inverse correlation between muscle  
223 glycogen content and AMPK activity has been established<sup>47, 72, 73</sup> [ENREF 34](#). AMPK has a glycogen  
224 binding domain on its  $\beta$ -subunit and there is evidence that glycogen- directly or indirectly- inhibits AMPK  
225 activity<sup>74</sup>. Furthermore, by tightly balancing ROS levels, PGC-1 $\alpha$  might antagonize the activation of ROS-  
226 dependent signaling pathways in skeletal muscle<sup>40, 75</sup>.

227 Those signaling pathways (AMPK, ROS and p38), however, mediate contraction-induced glucose uptake  
228 and metabolism. Indeed, the inhibition of AMPK abolishes glucose uptake in response to muscle  
229 contraction and similarly, inhibition of ROS-p38 prevents glucose uptake induced by muscle stretching<sup>76</sup>,  
230 <sup>77</sup>. It could be argued that the higher GLUT4 (Glucose Transporter 4) content in muscles of PGC-1 $\alpha$   
231 transgenic animals compensates the lack of AMPK and ROS-p38 mediated glucose uptake. However, the  
232 relative increase in glucose uptake is smaller in transgenic animals with ectopic expression of PGC-1 $\alpha$   
233 (~50%) than the increase in response to contraction (> 100%)<sup>46, 78-80</sup>.

234  
235 Oscillations of muscle glycogen and triglyceride levels occur with physical activity-rest cycles. Energy  
236 stores are depleted during physical activity and replenished during rest. Contraction and epinephrine  
237 activate the lipolysis of IMCL by activating hormone sensitive lipase (HSL) and by promoting the  
238 translocation of HSL to IMCL in skeletal muscle, thereby contributing to the temporary reduction in  
239 muscular triglyceride stores<sup>81, 82</sup>. Similarly, exercise stimulates glycogen breakdown<sup>83</sup>.

240 In contrast, PGC-1 $\alpha$ , besides promoting oxidative capacity, drives *de-novo* lipogenesis and lipid storage  
241 into IMCL in the sedentary state<sup>46</sup>. Furthermore, PGC-1 $\alpha$  stimulates glycogen synthesis and restrains  
242 glycogen breakdown<sup>47</sup>.

243 Ectopic expression of PGC-1 $\alpha$  in the absence of physical activity thus results in a stalling of glycogen and  
244 triglyceride stores at high levels in skeletal muscle<sup>46, 47</sup>. Analogously to an imbalance in energy intake and  
245 expenditure, the absence of physical activity leads to an imbalance between physical activity and rest.  
246 However, these physical activity-rest cycles are the core catalysts to physiologically break the stalling of  
247 muscle glycogen and triglyceride stores at high levels<sup>18</sup>.

248  
249 Moreover, energy expenditure of muscle is high during exercise, due to the low efficiency of muscular  
250 contraction (~25%) and thus the dissipation of the bulk of energy as heat. Therefore, although PGC-1 $\alpha$   
251 increases energy expenditure in muscle cells<sup>54, 55</sup>, this contribution to total energy expenditure might be  
252 relatively low in the absence of physical activity. Indeed, whole body energy expenditure is not elevated  
253 in sedentary mice with ectopic expression of PGC-1 $\alpha$ <sup>49</sup>.

254  
255 Importantly, exercise also affects other tissues and thus alters whole-body glucose homeostasis differently  
256 than muscle-specific activation of PGC-1 $\alpha$  alone<sup>84</sup>. An acute bout of exercise is associated with changes in  
257 the metabolism of liver and adipose tissue that result in an increased provision of fuel for the contracting  
258 muscle. The liver increases the release of glucose (initially derived from glycogenolysis and later from  
259 gluconeogenesis) into the circulation and adipose tissue increases the hydrolysis triglycerides and the  
260 release of long chain nonesterified fatty acids (LCFA) into the circulation. A large body of evidence from  
261 both humans and experimental animals has linked these changes to activation of the sympathetic nervous  
262 system (norepinephrine) and to increases in plasma levels of glucagon and epinephrine<sup>74</sup>. Regular exercise  
263 induces increases in AMPK and ACC phosphorylation in visceral adipose tissue and liver<sup>74</sup>. Despite the  
264 scarcity of literature concerning the heart, similar effects are expected to occur in the heart, where acute  
265 bouts of exercise promote elevated AMPK phosphorylation<sup>85</sup>. Furthermore, chronic exercise affects

266 mitochondrial biogenesis and thus respiration not only in skeletal muscle, but also in adipose tissue, liver,  
267 brain, kidney and cardiac muscle<sup>86-89</sup> [ENREF 84](#).

268  
269 It is thus conceivable, that PGC-1 $\alpha$  increases the capacity of skeletal muscle for substrate catabolism and  
270 anabolism, but does probably not substantially alter whole body energy expenditure and metabolic cycling  
271 in the absence of exercise (Figure 2).

272  
273 **Current limitations for pharmaceutical targeting of PGC-1 $\alpha$**

274 Our current knowledge of the action of PGC-1 $\alpha$  derives mainly from genetic mouse models. The hormetic  
275 effect of PGC-1 $\alpha$  on skeletal muscle function and integrity emerged as an important insight from these  
276 studies in transgenic animals<sup>90</sup>. In mouse models with moderate, physiological expression of PGC-1 $\alpha$   
277 (levels comparable to those of an oxidative soleus muscle), PGC-1 $\alpha$  was deemed a beneficial modulator of  
278 muscle plasticity, while higher levels resulted in adverse effects such as impairments in muscular glucose  
279 homeostasis and atrophy<sup>90-92</sup>.

280  
281 A future challenge is the development of safe drugs that increase PGC-1 levels specifically in skeletal  
282 muscle to exactly predefined levels<sup>93</sup>. Currently known substances that pharmacologically target PGC-1 $\alpha$   
283 are either unspecific or associated with side effects. Metformin and other agents which stimulate AMP-  
284 activated kinase, PPAR $\delta$  (Peroxisome Proliferator-Activated Receptor) agonists, corticosteroids and  $\beta$ -  
285 adrenergic agonists have all been shown to increase PGC-1 $\alpha$ <sup>94</sup>. However, they are all unspecific and  
286 furthermore affect PGC-1 $\alpha$  levels in the liver, where PGC-1 $\alpha$  enhances gluconeogenesis and hepatic  
287 glucose output<sup>95</sup>. Moreover, they potentially also activate PGC-1 $\alpha$  in the heart, thereby leading to  
288 derangements of mitochondrial ultrastructure and development of cardiomyopathy<sup>96</sup>. The cardiomyopathy  
289 is characterized by an increase in ventricular mass and chamber dilatation and seems to be reversible<sup>96</sup>.

290  
291 **Conclusion and outlook**

292 PGC-1 $\alpha$  evidentially confers a trained state upon skeletal muscle and increases the metabolic capacity  
293 without inflicting *per se* positive effects on body weight control and glucose homeostasis when  
294 exclusively augmented in this tissue<sup>25, 40, 49, 57</sup>. However, elevated levels of PGC-1 $\alpha$  in skeletal muscle can  
295 serve to support and facilitate exercise in physically inactive subjects. This is essentially based on the  
296 direct demonstration that sedentary mice with ectopic expression of PGC-1 $\alpha$  have a higher endurance  
297 capacity when they are forced to run and their isolated muscles are resistant to fatigue<sup>34, 35, 57</sup> [ENREF 33](#).  
298 Many additional effects of exercise, which are crucial for metabolic health, cannot simply be mimicked by  
299 the sole induction of PGC-1 $\alpha$ . A trigger, such as exercise, is mandatory to increase energy expenditure and  
300 to initiate metabolic cycling. In the absence of this trigger, PGC-1 $\alpha$  might even exert detrimental effects  
301 by promoting stalling of muscular energy stores at high levels<sup>46, 47</sup>.

302  
303 The combination of targeting PGC-1 $\alpha$  to facilitate exercise and a moderate, tolerable level of exercise to  
304 avoid energy conservation and initiate metabolic cycling might constitute a promising approach for the  
305 treatment of obesity, obesity-associated comorbidities and for long-term body weight control. Importantly,  
306 this approach is not restricted to patients with metabolic impairments, but is broadly applicable for other  
307 diseased states where weight regain can occur, but where the health status of the patient precludes  
308 achievement of adequate levels of physical activity. More specifically, such weight regain in the form of  
309 preferential catch-up-fat is well documented after weight loss due to malnutrition, cancer, septic shock or  
310 AIDS and thus constitutes a general phenomenon related to weight loss<sup>17</sup>.

311  
312 The potential for such combined treatments might be enormous. The pinnacle for the global prevalence of  
313 metabolic disorders has definitely not yet been reached. Future technical developments will further  
314 decrease the necessity for daily physical activity and lead to an even more sedentary behavior. An entire  
315 evolving scientific branch is dedicated to the investigation of such ‘inactivity physiology’<sup>97, 98</sup>. A recent  
316 review on the subject addresses the risk of sitting in decreasing energy expenditure by diminishing non-  
317 exercise activity thermogenesis and favoring the development of metabolic diseases and a recent study



318 reported attenuated insulin sensitivity in healthy, non-exercising subjects who went from a normal to a  
319 low level of ambulatory activity for 2 wks<sup>97, 99</sup> [ENREF 77](#). In the light of the increasing prevalence of  
320 metabolic disorders, the use of adjuvants to enhance exercise effects in people with a low drive to move  
321 might therefore gain profound interest for public health management in the coming years.

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### 326 **Conflict of interest**

327 The authors declare no conflict of interest. Our research is supported by grants from the Swiss National  
328 Science Foundation (SNF PP00A-110746), the Muscular Dystrophy Association USA (MDA), the  
329 SwissLife ‘Jubiläumsstiftung für Volksgesundheit und medizinische Forschung’, the Swiss Society for  
330 Research on Muscle Diseases (SSEM), the Swiss Diabetes Association, the Roche Research Foundation,  
331 the United Mitochondrial Disease Foundation (UMDF), the Association Française contre les Myopathies  
332 (AFM), and the University of Basel. The funders had no role in the preparation of the manuscript.

333

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708 **Figure legends**

709 **Figure 1: Cycles of famine/feast (outer cycle) and physical activity/rest (inner cycle).** Reductions in  
710 energy intake (famine or dieting) induce weight and adipose tissue loss. Concomitantly, the reduced food  
711 availability prompts ambulatory activity for the purpose of gathering and hunting. This additionally  
712 contributes to weight and fat mass loss. Moreover, physical activity depletes ATP, glycogen and IMCL  
713 stores in skeletal muscle. The scarcity of energy ultimately activates a thrifty program in skeletal muscle  
714 to conserve energy.

715 If food becomes available (feast) and dieting is abandoned, the thrifty program supports the replenishment  
716 of energy stores and weight regain, which preferentially occurs in the form of catch-up fat and which is  
717 driven by a hyperinsulinemic state. Satiety signals during the period of feast automatically lead to rest,  
718 which further supports adipose tissue regain and the restoration of glycogen and IMCL pools in the  
719 muscle.

720 Exercise can counteract the energy conservation in skeletal muscle and prevent weight regain. In addition,  
721 regular exercise promotes the turnover of ATP, glycogen and IMCLs. The effects of exercise are indicated  
722 as dotted lines.

723 **Figure 2: PGC-1 $\alpha$  and exercise.** Acute bouts of exercise raise myoplasmic calcium levels, increase the  
724 activity of p38 and AMPK, and generate reactive oxygen and nitrogen species, which ultimately all  
725 culminate in activation of PGC-1 $\alpha$ . Subsequently, PGC-1 $\alpha$  carries out its various functions.

726 The ectopic expression of PGC-1 $\alpha$  alone- even in the absence of exercise- is largely sufficient to mimic  
727 exercise-like responses. PGC-1 $\alpha$  favors higher myoplasmic calcium and nitric oxide levels by slowing  
728 down calcium handling and inducing nitric oxide synthase expression, respectively. Muscle PGC-1 $\alpha$   
729 promotes mitochondrial biogenesis, fiber-type switching and angiogenesis. Furthermore, PGC-1 $\alpha$   
730 increases glucose uptake in order to generate ATP for later muscle contraction as well as to fuel glycogen

731 and IMCL stores. In the absence of physical activity, this will result in elevated levels of ATP, glycogen  
732 and IMCLs.

733 In contrast to the sole ectopic expression of PGC-1 $\alpha$ , the stimulation of p38, AMPK and ROS by muscle  
734 contraction, further increases glucose uptake to quickly generate additional ATP. Moreover, exercise  
735 depletes ATP, glycogen and IMCL stores during muscle contraction and thereby induces metabolic  
736 cycling between energy depletion during physical activity and energy refueling post-exercise. Due to the  
737 low efficiency of muscle work around 75% of the energy is dissipated as heat and therefore these  
738 processes increase energy expenditure. Upon exercise, the sympathetic nervous system is activated and  
739 releases epinephrine and other hormones. Subsequent lipolysis in adipose tissue diminishes fat mass. In  
740 addition, skeletal muscle releases myokines that can act on other tissues.

741 Continuous lines and boxes with continuous lines: exercise-effects mediated by PGC-1 $\alpha$ . Dotted lines and  
742 boxes with dotted lines: effects mediated by exercise, but not imitable by ectopic expression of PGC-1 $\alpha$ .



