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Modulation of PGC-1α activity as a treatment for metabolic and muscle-related diseases

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Abstract

Physical inactivity is a predisposing factor for various disease states including obesity, cardiovascular disease, as well as for certain types of cancer. Regular endurance exercise mediates several beneficial effects such as increased energy expenditure and improved skeletal muscle function, and has been suggested as a therapeutic strategy for both metabolic and muscle-related disorders. “Exercise mimetic” is a collective term for compounds that can pharmacologically activate pathways which are normally induced during skeletal muscle contraction, and that could be used in the treatment of metabolic or muscle related diseases. Two such experimental “exercise mimetics” are AICAR and resveratrol, which have both been extensively studied in the context of metabolic dysfunction and muscle wasting in rodent disease models. These compounds have been postulated to activate AMP-activated protein kinase (AMPK) and sirtuin 1 (SIRT1), respectively, in skeletal muscle, and to increase the activation of the peroxisome proliferator-activated receptor γ co-activator 1α (PGC-1α). PGC-1α can mediate several metabolic and functional adaptations in skeletal muscle in response to physical exercise and is therefore an interesting target for the development of new “exercise mimetic” drugs.
Introduction

While regular exercise is important to maintain health and longevity, physical inactivity predisposes for many chronic diseases of metabolic origin, such as obesity, type 2 diabetes mellitus (T2DM) and cardiovascular pathologies, as well as certain types of cancer [1]. Importantly, lack of physical activity is also a key element in the etiology of aging-associated dysfunctions, for example sarcopenia and cognitive impairment [2]. Endurance exercise has been successfully applied or suggested as a therapy in a wide array of metabolic and muscle-related disorders, for example in obese and T2DM patients [3], cancer-associated cachexia [4] and muscular dystrophies [5]. Considering the physiological impact of exercise training at the whole body level and its low cost, this strategy is a preferred choice to either surgical or pharmacological interventions in obese patients [6]. This approach however is not without inherent difficulties, since adherence to an exercise regime can be difficult to maintain, and the impairment of skeletal muscle function observed in patients suffering from diseases such as sarcopenia or muscular dystrophies can limit the use of exercise as therapy [5]. Hence, in some pathological contexts, it would be advantageous to pharmacologically activate the same pathways that are activated by muscle contraction and thus enhance the therapeutic effects of exercise. When the homeostasis of a resting muscle cell is perturbed during a contraction, several pathways are either activated or inhibited to mediate the adaptive response to exercise, both at a post-translational and transcriptional level (reviewed in [7]). The transcriptional response in skeletal muscle to a single bout of exercise in humans can influence the expression of more than 900 genes, resulting in adaptive changes in mitochondrial metabolism, angiogenesis, β-oxidation and inflammation [7,8]. A key mediator of these transcriptional changes and a main point of convergence for different signaling events taking place in a contracting muscle is the peroxisome proliferator-activated receptor γ co-activator 1α (PGC-1α) [9]. Skeletal muscle PGC-1α is increased during exercise in humans [10] and can drive a slow oxidative gene program through the activation of several transcription factors such as estrogen-related receptor α (ERRα), nuclear respiratory factor 1/2 (NRF-1/2) and transcription factor A, mitochondrial (TFAM) [7,9]. In response to an energy stress such as muscle contraction, PGC-1α can be activated by two important energy sensors: AMP-activated protein kinase (AMPK) and sirtuin 1 (SIRT1) [11] (Fig. 1). AMPK is allosterically activated by both ADP and AMP during energy deficits, and positively regulates ATP-production through phosphorylation of metabolic enzymes [12]. Interestingly, AMPK also confers long-term transcriptional adaptations in response to energy stress, by phosphorylation and activation of several transcription factors as well as transcriptional co-activators, including PGC-1α [13]. Another important energy sensor during muscle contraction is SIRT1, a member of the SIRT family of class III deacetylases. SIRT1 senses perturbations in the NAD+/NADH ratio in muscle cells during exercise, and can mediate adaptive changes in mitochondrial function through deacetylation and activation of PGC-1α, as well as
through direct deacetylation of several transcription factors [14]. The central role for AMPK and SIRT1 as energy sensors in skeletal muscle, as well as the presence of pharmacological activators of these two enzymes, makes them attractive targets for possible “exercise mimetics”. This review will highlight the therapeutic potential of such putative “exercise mimetics”, as well as the implications of using direct PGC-1α activation as a treatment for metabolic and muscle-related disorders.

**AMPK / AICAR**

AMPK is activated in skeletal muscle during exercise and mediates both acute and long term metabolic adaptations to cope with the increased energy demand. Interestingly, in obese and type 2 diabetic individuals, activation of skeletal muscle AMPK during exercise is blunted [15]. This reduced activity of AMPK was also present in obese mice, and was further associated with reduced exercise capacity and diminished glucose uptake into skeletal muscle cells [16]. In this context, it therefore would be useful to enhance the positive effects of endurance training in obese patients by pharmacological activation of AMPK in skeletal muscle. One potential candidate for this is AICAR (5-Aminoimidazole-4-carboxamide ribonucleotide), an AMP analog that can activate AMPK in vivo [13]. AICAR administration has been shown to reduce obesity and improve glucose homeostasis in mice [17] and to increase glucose uptake in skeletal muscle of both healthy and T2DM patients [18], which reflect the potential therapeutic use of AICAR as an “exercise mimetic”. Importantly, AICAR can boost PGC-1α transcription and posttranslational modifications in skeletal muscle [19]. Thereby, AICAR enhances endurance performance and energy expenditure through increased transcription of mitochondrial and metabolic genes in sedentary mice [20]. PGC-1α played a central role in mediating these “exercise mimetic” effects of AMPK activation, since at least some genes activated by AICAR administration have been demonstrated to be dependent on PGC-1α [21]. Due to the beneficial effects on skeletal muscle function and metabolism, AICAR has also been studied in the context of muscular dystrophies and muscle wasting. In angiotensin II-mediated muscle wasting in mice, daily AICAR administration could normalize AMPK activity and thereby reverse the loss of skeletal muscle mass [22]. In contrast, AICAR could not attenuate the decrease in muscle mass induced by denervation in mice, even though PGC-1α expression and mitochondrial protein content in atrophic muscles were normalized [23]. These divergent effects of AICAR on attenuation of skeletal muscle wasting could be dependent on the different etiologies of these two atrophic mouse models, and would represent a variable therapeutic effect of AICAR depending on the nature of the muscle wasting disorder. In several recent papers, AICAR has been used to treat mdx mice, a model for Duchenne muscular dystrophy (DMD). In this model, AICAR administration improved skeletal muscle function through pleiotropic effects including increased mitochondrial activity, reduced inflammation...
and increased mitophagy [24-26]. Furthermore, AICAR treatment in combination with the peroxisome proliferator-activated receptor δ (PPARδ) agonist GW1516 was shown to potentiate AMPK-activity during concomitant exercise in mdx mice [27], and could prove effective in enhancing beneficial effects of exercise in DMD patients.

Thus, in summary, AMPK activation in skeletal muscle by AICAR can lead to several beneficial effects in obese and diabetic mouse models. In atrophic and dystrophic mouse models, AICAR can improve muscle function and mitochondrial activity, although attenuation of skeletal muscle loss could not be demonstrated in all atrophic mouse models.

SIRT1 / resveratrol

Resveratrol (RSV) is a naturally occurring antioxidant that activates SIRT1 in vivo, and thereby promotes PGC-1α deacetylation [28,29]. In obese sedentary mice, RSV improves exercise performance, ameliorates metabolic dysfunction and extends lifespan [28,29]. RSV could also boost mitochondrial adaptations in skeletal muscle in response to exercise [30,31], and some of these additive effects of RSV and exercise were further demonstrated to be dependent on skeletal muscle SIRT1 [31]. These findings have made RSV an interesting candidate for treating obesity and T2DM also in human subjects. In a recent clinical study, oral RSV administration did not affect either body weight or insulin sensitivity in obese patients [32], although in a similar study, RSV supplementation mediated mild metabolic adaptations combined with an increased transcription of mitochondrial genes in skeletal muscle [33]. In T2DM patients on the other hand, RSV administration has shown potential to improve glycemic control and insulin sensitivity [34,35]. RSV has also been investigated as a potential treatment for muscle wasting. In a rat model of mechanical unloading, RSV administration could prevent the decline in skeletal muscle oxidative capacity [36], and attenuate the loss of skeletal muscle strength induced by muscle disuse [36,37]. RSV was also found to attenuate skeletal muscle wasting in a mouse model for cancer-associated cachexia, an effect that was associated with a reduced nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) activation and a reduction in muscle RING-finger protein 1 (MuRF1) expression [38]. The protective effects of RSV in these mouse models of skeletal muscle atrophy could be attributed to the activation of PGC-1α, since this co-activator has been shown to reduce NFκB driven transcription and attenuate activation of atrophic pathways in skeletal muscle [23,39]. Similar to AICAR, RSV has also been studied in the context of muscle dystrophy. In dystrophic mdx mice, RSV could attenuate the decline in skeletal muscle mass [40] and fatigue resistance [41], but could not ameliorate the ongoing inflammation or muscle injury [40]. In contrast, a different study in young mice could demonstrate an
ameliorating effect of RSV treatment also on the infiltration of inflammatory cells into dystrophic muscle [42].

Thus, RSV administration has shown therapeutic potential for both metabolic and muscle wasting disorders in mice, while in human obese subjects, the beneficial effects of oral RSV administration are so far less promising.

PGC-1α – a central regulator in exercise

Physical exercise induces a wide range of signaling pathways, all contributing to the metabolic and functional adaptations of skeletal muscle. The beneficial effects of activating a single one of these pathways through pharmacological modulation of either AMPK or SIRT1 have been demonstrated in several rodent disease models. This approach to designing “exercise mimetics” has yielded encouraging results, but considering the complex response to exercise in skeletal muscle, these compounds could only be considered as partial “exercise mimetics”. A more complete “exercise mimetic” would instead directly target a central effector that could mediate both metabolic and functional adaptations to exercise in the skeletal muscle, and one such potential target would be PGC-1α.

Skeletal muscle PGC-1α drives several gene programs that are important for muscle adaptation to endurance exercise. This is evident in mice overexpressing PGC-1α specifically in skeletal muscle, which demonstrate a shift towards a slow-twitch oxidative phenotype, characterized by an increased mitochondrial biogenesis and higher fatigue resistance [43]. These changes are consistent with what has been observed in humans during acute endurance exercise, where an increase in PGC-1α was associated with a slow type muscle fiber phenotype [10]. PGC-1α can also regulate other processes that are important for exercise adaptation, such as muscle fatigue resistance and force generation [44], adaptation of the neuromuscular junction [45], angiogenesis [46], as well as glycogen storage [47]. PGC-1α overexpression in skeletal muscle of mice resulted in an increased endurance capacity combined with a higher utilization of lipids as energy substrate during exercise [48]. The opposite was seen in mice carrying a skeletal muscle-specific knockout of PGC-1α, where exercise performance was reduced [49]. Mice deficient for skeletal muscle PGC-1α also displayed increased muscle damage after an acute exercise bout [49], demonstrating an important role for PGC-1α in maintaining muscle integrity during exercise. PGC-1α acts as a convergence point for many signaling events taking place in a contracting skeletal muscle, and drives a pleiotropic transcriptional response resulting in improved muscle metabolism and endurance capacity. This makes modulation of PGC-1α an interesting target for the treatment of metabolic and muscle related diseases.
PGC-1α – a potential target for “exercise mimetics”

An important factor in the prevention and treatment of obesity is to increase energy expenditure. Importantly, resting energy expenditure is increased up to 48 hours after an acute exercise bout in humans [50]. Irisin, a myokine released from skeletal muscle during exercise is an obvious candidate to mediate this effect, since it has been shown to increase whole body energy expenditure through enhanced mitochondrial uncoupling in white adipose tissue [51]. PGC-1α regulates the transcription of irisin in skeletal muscle, and in PGC-1α muscle knockout mice, circulating plasma levels of this myokine were accordingly reduced [51]. Interestingly, in contrast to the increased resting whole body energy expenditure seen in mice with an ectopic overexpression of irisin in liver [51], no positive effect on this parameter could be demonstrated in chow fed mice overexpressing PGC-1α in skeletal muscle [48,52]. These results could indicate a minor role for skeletal muscle PGC-1α in the regulation of energy expenditure through irisin during physical inactivity, while still being able to modulate energy expenditure during exercise. This suggestion is further corroborated by the increased peak oxygen consumption seen in PGC-1α transgenic mice during acute exercise [48].

In mice fed a high fat diet, increased skeletal muscle PGC-1α was not followed by increased resting energy expenditure, altered weight gain or improved glucose and insulin levels [52]. Surprisingly, overexpression of PGC-1α in muscle was instead even found to have a detrimental effect on insulin stimulated glucose uptake in high fat diet fed sedentary mice [52]. This increased insulin resistance was attributed to an increased uptake of fatty acids into muscle, which exceeded the capacity of mitochondrial lipid oxidation, and that combined with elevated de novo lipogenesis, resulted in increased intramuscular lipid storage and a concomitant reduction in skeletal muscle insulin sensitivity [52]. Importantly however, when these mice received a continuous exercise intervention during the high fat feeding, these detrimental effects were reversed, and muscle glucose uptake as well as whole body glucose homeostasis was improved [53], demonstrating a synergistic effect of physical exercise and PGC-1α overexpression on glucose homeostasis. By increasing PGC-1α in skeletal muscle, the metabolic flexibility in the muscle is increased, mimicking what has been demonstrated during physical exercise. These changes include an up-regulation of mitochondrial fat oxidation [54], but also shunting of glucose away from oxidation, towards glycogen synthesis [47] and lipogenesis [55]. Thus, if PGC-1α activity was increased in skeletal muscle of sedentary individuals, this could potentially lead to an uncoupling of the anabolic re-fueling processes induced by exercise from the increase in energy expenditure during muscle contraction. In a sedentary obese state where circulating lipid levels are already increased, activation of PGC-1α might result in
exacerbated intramuscular lipid accumulation and peripheral insulin resistance. These results strongly suggest that using PGC-1α as an “exercise mimetic” for the treatment of obesity and T2DM in the absence of actual physical activity could potentially worsen the metabolic dysfunction in skeletal muscle as well as at a whole body level.

However, activation of PGC-1α might still prove to be a valid therapeutic option in the context of metabolic dysfunctions that are not primarily associated with increased obesity. One such example is during aging, where overexpression PGC-1α in skeletal muscle of mice was shown to ameliorate aging-associated insulin resistance and improve the metabolic flexibility of aged skeletal muscles [56]. In aged mice, increased PGC-1α expression also improved muscle function and endurance capacity in conjunction with reduced sarcopenia [56]. A similar protective role of PGC-1α in skeletal muscle atrophy was also seen in fasting- and denervation-induced atrophy, where PGC-1α overexpression could rescue oxidative capacity and reduce the induction of a transcriptional atrophic response in the muscle [39]. This effect of PGC-1α was proposed to occur through inhibition of forkhead box O3 (FoxO3) and NFκB driven transcription of atrophy-specific ubiquitin ligases, leading to a reduction in proteolysis [23]. The ability of PGC-1α to inhibit NFκB driven transcription has also recently been demonstrated for expression of pro-inflammatory cytokines in skeletal muscle [57]. In mice suffering from cancer-induced cachexia, PGC-1α overexpression up-regulated mitochondrial biogenesis, but did not prevent the reduction in body weight and muscle mass associated with the disease [58]. Interestingly, the authors could also show that increased levels of PGC-1α in skeletal muscle caused an increase in tumor size, an effect that was speculated to occur through growth-promoting myokines and could potentially limit the potential therapeutic use of PGC-1α activation in this context [58]. In dystrophic mdx-mice on the other hand, transgenic PGC-1α overexpression reduced muscle damage and improved muscle function [45]. These effects were also demonstrated in mice subjected to PGC-1α gene transfer into dystrophic muscles, resulting in a fast-to-slow fiber type switch, increased expression of utrophin and increased satellite cell activation [41,59]. Increased muscle PGC-1α also demonstrated a therapeutic potential in a mouse model for amyotrophic lateral sclerosis (ALS), where it could improve muscle function and endurance capacity of the mice even in the later stages of the disease, unfortunately in the absence of a positive effect on lifespan of the mice [60].

These results demonstrate a strong potential for PGC-1α to attenuate muscle wasting in several etiologically distinct disease states, and furthermore to improve both the metabolic phenotype and function of the affected muscles.
Conclusions

The potential of using AICAR and RSV to mimic exercise through activation of exercise-induced pathways in the sedentary skeletal muscle have shown therapeutic beneficial effects in both metabolic and muscle-related diseases (Table 1). Since it is hard to mimic all the metabolic, neuronal as well as mechanical stimuli that occur during an actual muscle contraction, these “exercise mimetic” compounds could instead be administered in combination with physical activity to enhance the therapeutic potential of exercise. A direct effect of such an “exercise enhancer” would be to boost the activation of certain pathways during exercise, and thereby increase the beneficial adaptations to exercise in the muscle, a method that has proven to be successful for both RSV treatment [30,31] and PGC-1α activation [53]. On the other hand, in conditions where skeletal muscle dysfunction is a central part of the disease etiology, administration of an “exercise enhancer” to these patients could increase mobility and the ability to perform physical activities, and thereby improve life quality. The fact that PGC-1α can activate gene programs associated with both mitochondrial and functional adaptations in skeletal muscle, makes it an important potential candidate for treatment of diseases where reduced muscle function is a main part of the etiology. In line with this, increased levels of PGC-1α in skeletal muscle have been shown to ameliorate the decline in muscle function in mouse models associated with muscle-wasting diseases such as DMD [45] and ALS [60], as well as in aging [56] (Table 1). On the other hand, in metabolic diseases such as obesity and T2DM, PGC-1α activation could instead prove to be detrimental, since it activates lipid refueling in skeletal muscle without a concomitant increase in energy expenditure, which could potentially exacerbate insulin resistance.

Therefore, activation of PGC-1α in skeletal muscle could represent a potential way to improve muscle function in atrophic diseases, but could on the other hand be less suitable as a treatment for obesity in the absence of actual physical exercise. Finally, it is important to note that the experimental “exercise mimetics” AICAR, RSV and PPARδ ligands [20] have several potential drawbacks that hinder broad application in humans, such as poor oral bioavailability and unwanted side-effects that could complicate chronic treatment [61]. Furthermore, it is debatable whether real “exercise mimetics” can even be developed [62]. Therefore, until such therapeutically deployable compounds are found, bona fide physical activity remains a cheap, yet effective intervention of choice for many diseases.
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Figure Legend

**Figure 1. Schematic representation of the processes involved in AMPK- and SIRT1-mediated activation of PGC-1α.**

During physical exercise AMPK and SIRT1 are activated in skeletal muscle. Cross-talk between these two proteins occurs through SIRT1-mediated deacetylation of the AMPK-kinase LKB1, and through the ability of AMPK to raise intracellular NAD+ levels to activate SIRT1 [11]. Coordinated activation of AMPK and SIRT1 leads to activation of PGC-1α through AMPK-mediated phosphorylation and subsequent deacetylation by SIRT1. PGC-1α then interacts with several transcription factors, to mediate the induction of gene programs important for skeletal muscle adaptation to exercise (see box), through either direct or indirect transcriptional modulation. AICAR and resveratrol are pharmacological compounds that can activate AMPK and SIRT1 respectively, and thereby increase activation of PGC-1α in skeletal muscle. Due to their ability to activate signaling pathways normally induced during physical exercise, AICAR and resveratrol have been termed “exercise mimetics” [61].

**Abbreviations:** TF, transcription factor; LKB1, liver kinase B1; NAD+, Nicotinamide adenine dinucleotide; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1-α; NMJ, neuromuscular junction; Esrra, estrogen-related receptor α; Tfam, transcription factor A, mitochondrial; Cycs, cytochrome complex; Vegf, vascular endothelial growth factor; Angpt2, angiopoietin-2; Pdgfb, platelet-derived growth factor subunit B; AChRα, acetylcholine receptor α; Utrn, utrophin; Gabpa, GA-binding protein alpha chain; Fasn, fatty acid synthase; Dgat, diglyceride acyltransferase; Gpam, mitochondrial glycerol-3-phosphate acyltransferase; Atp2a1, sarco/endoplasmic reticulum Ca2+-ATPase 1; Casq1, calsequestrin 1; Casq2, calsequestrin 2; Ldha, lactate dehydrogenase a; Ldhb, lactate dehydrogenase b; Slc16a1, monocarboxylate transporter 1.

**Denotations:** (P), phosphorylation; (Ac), acetylation; ↑, up-regulation; ↓, down-regulation.
- Mitochondrial function
  \( (Esrra \uparrow, Tfam \uparrow, Cycs \uparrow) \) [54]
- Angiogenesis
  \( (Vegf \uparrow, Angpt2 \uparrow, Pdgfb \uparrow) \) [46]
- NMJ remodeling
  \( (AChR\alpha \uparrow, Utm \uparrow, Gabpa \uparrow) \) [45]
- De novo lipogenesis
  \( (Fasn \uparrow, Dgat \uparrow, Gpam \uparrow) \) [55]
- Calcium handling
  \( (Atp2a1 \downarrow, Casq1 \downarrow, Casq2 \uparrow) \) [44]
- Lactate homeostasis
  \( (Ldha \downarrow, Ldhb \uparrow, Slc16a1 \uparrow) \) [64]
Table 1. Effects of AICAR, resveratrol and PGC-1α overexpression on metabolism and muscle function in rodent disease models.

<table>
<thead>
<tr>
<th>Disease models</th>
<th>AICAR</th>
<th>Resveratrol</th>
<th>PGC-1α overexpression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity / Type 2 diabetes</td>
<td>Obesity ↓ (17)</td>
<td>Insulin sensitivity ↑ (28, 29)</td>
<td>Intramuscular lipid storage ↑ (52)</td>
</tr>
<tr>
<td></td>
<td>Insulin sensitivity ↑ (17)</td>
<td>Exercise performance ↑ (28)</td>
<td>in combination with exercise</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Life span ↑ (29)</td>
<td>Glucose homeostasis ↑ (53)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Insulin sensitivity ↑ (52)</td>
</tr>
<tr>
<td>Aging</td>
<td>Not determined</td>
<td>Mitochondrial activity ↔ (63)</td>
<td>Insulin sensitivity ↑ (56)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Muscle wasting ↔ (63)</td>
<td>Exercise performance ↑ (56)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Muscle wasting ↓ (56)</td>
</tr>
<tr>
<td>Angiotensin II induced atrophy</td>
<td>Muscle wasting ↓ (22)</td>
<td>Not determined</td>
<td>Not determined</td>
</tr>
<tr>
<td>Disuse/denervation induced atrophy</td>
<td>Mitochondrial proteins ↑ (23)</td>
<td>Oxidative capacity ↑ (36)</td>
<td>Mitochondrial activity ↑ (58)</td>
</tr>
<tr>
<td></td>
<td>Muscle wasting ↔ (23)</td>
<td>Muscle force ↑ (36, 37)</td>
<td>Muscle wasting ↔ (58)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tumor size ↑ (58)</td>
</tr>
<tr>
<td>Cancer-associated cachexia</td>
<td>Not determined</td>
<td>Muscle wasting ↓ (38)</td>
<td>Muscle wasting ↓ (38)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duchenne muscular dystrophy (DMD)</td>
<td>Mitochondrial proteins ↑ (24-25)</td>
<td>Muscle wasting ↓ (40)</td>
<td>Muscle function ↑ (41, 45, 59)</td>
</tr>
<tr>
<td></td>
<td>Muscle weight ↑ (25)</td>
<td>Inflammation ↓ (42)</td>
<td>Muscle damage ↓ (41, 45, 59)</td>
</tr>
<tr>
<td></td>
<td>Inflammation ↓ (25)</td>
<td>Muscle function ↑ (41)</td>
<td></td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis (ALS)</td>
<td>Not determined</td>
<td>Not determined</td>
<td>Muscle function ↑ (60)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Exercise performance ↑ (60)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Life span ↔ (60)</td>
</tr>
</tbody>
</table>

**Abbreviations:** PGC-1α, peroxisome proliferator-activated receptor γ co-activator 1α

**Denotations:** (↑) indicates an increase and (↓) indicates a decrease of the described process/phenotype in treated/transgenic mice compared to untreated/wild-type mice. (↔) indicates no difference between treated/transgenic mice and untreated/wild-type mice.