Elucidating exercise-induced skeletal muscle signaling pathways and applying relevant findings to preemptive therapy for lifestyle-related diseases

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Abstract. While it is well recognized that exercise represents a radical preventive and therapeutic measure for lifestyle-related diseases, it is clear that contemporary lifestyles abound with situations where exercise may be found difficult to implement on a continuous basis. Indeed, this has led to global expectations for elucidation of the exercise-activated skeletal muscle signaling pathways as well as for development of exercise mimics that effectively activate such pathways. It is shown that exercise activates the transcriptional coactivator PGC-1α via AMPK/SIRT1 in muscle, thereby not only enhancing mitochondrial function and muscle endurance but upregulating energy metabolism. Further, adipocyte-derived adiponectin is also shown to activate AMPK/SIRT1/PGC-1α via its receptor AdipoR1 in skeletal muscles. Thus, adiponectin/AdipoR1 signaling is thought to constitute exercise-mimicking signaling. Indeed, it has become clear that AMPK, SIRT1 and AdipoR activators act as exercise mimetics. With the crystal structures of AdipoR elucidated and humanized AdipoR mice generated toward optimization of candidate AdipoR-activators for human use, expectations are mounting for the clinical application in the near future of AdipoR activators as exercise mimetics in humans. This review provides an overview of molecules activated by exercise and compounds activating these molecules, with a focus on the therapeutic potential of AdipoR activators as exercise mimetics.

Key words: Exercise mimetics, AdipoR, AdipoR activators

Exercise-induced Glucose/lipid Metabolism

Glucose and lipids represent a primary source of skeletal muscle energy, with their metabolic balance masterfully regulated in response to nutritional status and locomotor stimulation. While glucose represents a primary source of energy in favorable nutritional status, lipids also represent an energy source in a fasting state or during aerobic exercise associated with elevation of free fatty acids. In the latter state, an appropriate shift from glucose to lipids as an energy source is not only essential to ensuring a constant supply of glucose to brain and other tissues thus maintaining life; it also plays an extremely important role in inducing the body to burn off excess fat thereby reducing body fat.

Disruption of the proper glucose-lipid metabolic balance is a hallmark feature of type 2 diabetes, which occurs with changes in lifestyle and presents as a state of decreased, insulin-dependent, glucose uptake by skeletal muscle (i.e., insulin resistance). In contrast, locomotor stimulation is shown to promote glucose uptake and metabolism (acute effects of exercise) even in a state of insulin resistance, while decreases in body fat associated with routine moderate exercise are shown to improve insulin resistance, impaired glucose tolerance, and blood lipid composition (i.e., chronic effects of exercise). Thus, while it has long been recognized that exercise-mediated normalization of the glucose-lipid metabolic balance in the skeletal muscle contributes a great deal toward metabolic correction in individual humans, recent research has only begun to unravel in detail the molecular mechanisms of exercise-induced effects on glucose/lipid metabolism which has remained a “black box”. Of these, one mediated by adipocyte-derived adiponectin [1-4], in which the expression and activation of PPAR-γ coactivator-1α (PGC-1α) is shown to be modulated via the adiponectin receptor AdipoR1 [5], while involving
Ca\(^{2+}\), AMP-activated protein kinase (AMPK) and SIRT1 signaling pathways, has drawn considerable attention [6].

**Types of Skeletal Muscle Fibers and Associated Glucose/lipid Metabolism**

Skeletal muscle fibers are broadly divided into type I fibers that support sustained movements (also known as slow-twitch muscle fibers) and type II fibers that support quick, powerful movements (also known as fast-twitch muscle fibers), with the latter further classified into type Iia fibers characterized by high oxidative enzyme activity and Iib fibers, a mixture of which are shown to be present in all muscles except for special muscles. It is a crucial aspect of energy metabolism that glucose/lipid metabolism takes place at a high rate in skeletal muscles containing a high proportion of type I and type Iia fibers with high oxidative enzyme activity thus accounting for high mitochondrial mass and activity. In contrast, anaerobic metabolic capacity is shown to be high enough to allow powerful movements, but aerobic metabolic capacity is shown to be low in skeletal muscles containing a high proportion of type Iib fibers. The mixture proportions of these different muscle fibers vary depending not only on the skeletal muscle tissue but on the kind and quality of exercise performed by the skeletal muscle tissue. For instance, performing sustained exercise on a continuous basis leads to an increase in the proportion of type I fibers in the skeletal muscle tissue [7]. On the other hand, it is also reported that a high proportion of type Iib muscle fibers, as well as a low proportion of type I and Iia fibers, is shown to be present in the skeletal muscle tissue of type 2 diabetic patients [8]. It is therefore assumed that increasing the proportion of type I fibers leads to an increase in mitochondrial number as well as in energy metabolism and thus represents a viable approach to prevention of obesity or type 2 diabetes.

It has been recognized in recent years that prevention of sarcopenia is crucial to the realization of a healthy longevity society. A coinage derived from the Latin words sarx (muscle) and penia (loss), sarcopenia refers to age-associated loss of muscle, which is typically characterized by selective atrophy of type II fibers [9]. As a preventive measure for sarcopenia, resistance exercise is shown to be effective, and one of its mechanisms is reported to be the activation of phosphatidylinositol-3 kinase/Akt/mammalian target of rapamycin (mTOR) signaling, which represents a typical intracellular signaling pathway involved in promoting muscle protein synthesis [10]. It is also known that, when activated, mTOR signaling promotes muscle enlargement through the 70 kDa ribosomal S6 kinase (p70S6K) and eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) [11].

It is also shown that performing appropriate aerobic exercise continuously leads to an increase in the proportion of type I fibers with high aerobic metabolic capacity, where this shift in skeletal muscle fiber type is shown to be induced by a composite of stimulations by various pathways activated by exercise, including Ca\(^{2+}\) signaling pathway, energy signaling, and mechanical stress. Of the putative molecules involved in transcriptional regulation downstream of these signaling pathways, PGC-1α is currently drawing considerable attention.

**Role and Significance of PGC-1α in skeletal Muscle Glucose Metabolism**

A molecule cloned by Spiegelman and colleagues, PGC-1α was initially reported to be expressed specifically in brown adipocytes [12]; however, it was subsequently reported by the same group that it is abundantly expressed in skeletal muscles and the liver as well. Furthermore, PGC-1α is shown to be preferentially expressed in soleus muscle containing a high proportion of type I fibers, of all skeletal muscles, with its expression shown to be increased during sustained exercise; it is also reported to be closely implicated in the exercise-induced shift in skeletal muscle fibers as well as in the regulation of mitochondrial mass and function.

In fact, it is shown that transgenic mice overexpressing PGC-1α specifically in skeletal muscles are associated with an increase not only in the amount of troponin I and myoglobin characteristic of type I fibers but in mitochondrial mass, thus accounting for increased exercise endurance [13].

It is also reported that type 2 diabetic patients are associated with decreased expression of oxidative phosphorylation genes and that PGC-1α has a role to play in regulating their expression levels [14]. Furthermore, it is reported that Mexican-Americans are associated with decreased expression of co-transcriptional regulation factors, such as PGC-1α, PGC-1β, and NRF-1, in skeletal muscles, despite being non-diabetic, if they have a family history of diabetes [15]. On the other hand, younger, healthy subjects with insulin resistance are reported to have no abnormalities in PGC-1α and its downstream molecules, despite exhibiting decreased mitochondrial function and density [16]. This highlights the fact that this study involved younger and non-obese subjects, in contrast to the other study cited above [15] which involved middle-aged and obese individuals. Thus, the possibility cannot be ruled out that obesity and aging contributed to decreased PGC-1α expression in these individuals.

Thus, research suggests that while non-PGC-1α-dependent pathways also come into play in skeletal
exercise-mimicking beneficial effects induced by R419 in the skeletal muscle of mice are various and entail improving insulin sensitivity and exercise endurance (Table 1).

Moreover, as their collateral benefit, exercise mimetics possibly induce muscle-secreted factors that are released into the circulation during and after exercise. It has been proposed that myokine production is at least part of the mechanism through which exercise exerts its systemic effects in tissues other than muscles. Myokines initially drew attention through findings on exercise and muscle-derived IL-6 [26]. Now, it is known that numerous cytokines, peptides and metabolites are released from contracting skeletal muscles during exercise [27]. It has also been shown that AICAR improves cognition and motor coordination, while both AICAR and GW501516 promote hippocampal neurogenesis and spatial memory without crossing the blood-brain barrier, suggesting that their effects in the brain may be mediated by muscle-derived factors [28, 29]. If amenable to treatment with drugs, such exercise-induced factors may represent further targets for the development of another class of exercise mimetics.

Most intriguingly, it has become clear that the adipocyte-secreted adipokines, leptin [30] and adiponectin [31] activate AMPK as well. It has also been shown that adiponectin enhances the expression of acyl CoA oxidase (ACO) involved in fatty acid oxidation, as well as of uncoupling protein (UCP) involved in fatty acid oxidation, in a mouse model of obesity/type 2 diabetes given adiponectin [32] or crossed with transgenic mice [33]. Additionally, using C2C12 cells as an in vitro model of skeletal muscle or AdipoR-deficient mice, research has shown that adiponectin activates skeletal muscle AMPK, thus promoting fatty acid oxidation and glucose uptake [31, 34] and that Ca$^{2+}$ signaling is part of the mechanisms of AMPK activation [6].

While AMPK is shown to be strongly activated in response to increases in AMP concentrations during exercise or fasting, there are two known pathways through which AMPK is activated, i.e., allosteric and AMP kinase (AMPKK)-mediated pathways. Of these, the AMPKK-mediated activation of AMPK primarily entails phosphorylation of threonine 172 (Thr172) in the α subunit of AMPK [35]. LKB1 and Ca$^{2+}$/calmodulin-dependent protein kinase β (CaMKK β) are also known as AMPKK as they activate AMPK [17, 36, 37]. While elevation of intracellular Ca$^{2+}$ concentrations is required for CaMKK β activation, experimental systems inducing forced AdipoR1 expression in C2C12 cells or Xenopus laevis oocytes or involving muscle-specific AdipoR1-deficient mice have demonstrated that adiponectin/AdipoR1 induces an influx of extracellular Ca$^{2+}$ thus...
activating AMPK via CaMKK β [6]. Furthermore, it has been shown that activated AMPK phosphorylates threonine 177 (Thr177) and serine 538 (Ser538) in PGC-1α, suggesting that phosphorylation of PGC-1α is crucial to activation of PGC-1α [6] (Fig. 1).

**AMPK-SIRT1-mediated deacetylation of PGC-1α**

In 2000, transcriptional silencing and longevity protein Sir2 has been shown to be an NAD-dependent deacetylase essential to lifespan regulation in budding yeast [38] with its orthologues also subsequently shown

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**Table 1  Therapeutic targets for exercise mimetics in enhancing skeletal muscles**

| Agents/Compounds       | Target molecules | Effects on skeletal muscles                                                                 | Clinical application | References |
|------------------------|------------------|-----------------------------------------------------------------------------------------------|----------------------|------------|
| Metformin              | AMPK             | · Increased glucose uptake<br>· Improved insulin sensitivity                                 | Yes                  | 22, 23, 24 |
| AICAR                  | AMPK             | · Increased glucose uptake<br>· Improved insulin sensitivity<br>· Increased mitochondrial biogenesis<br>· Conversion of the fiber composition from type II to type I<br>· Increased exercise endurance | No                   | 19, 20     |
| Cpd14                  | AMPK             | · Improved insulin sensitivity                                                                | No                   | 21         |
| R419                   | AMPK             | · Increased glucose uptake<br>· Improved insulin sensitivity<br>· Increased mitochondrial biogenesis<br>· Increased exercise endurance | No                   | 25         |
| Resveratrol            | SIRT1            | · Increased glucose uptake<br>· Improved insulin sensitivity<br>· Increased mitochondrial biogenesis<br>· Conversion of the fiber composition from type II to type I | No                   | 40         |
| Nicotinamide Riboside  | SIRT1            | · Improved insulin sensitivity<br>· Increased mitochondrial biogenesis<br>· Conversion of the fiber composition from type II to type I<br>· Increased exercise endurance | No                   | 44, 45     |
| AdipoRon               | AdipoR           | · Increased glucose uptake<br>· Improved insulin sensitivity<br>· Increased mitochondrial biogenesis<br>· Conversion of the fiber composition from type II to type I<br>· Increased exercise endurance | No                   | 46, 48     |

**Fig. 1  Signaling pathways shown to be induced by exercise and exercise mimetics**

Exercise and exercise mimetics are shown to activate the AdipoR/AMPK/SIRT1/PGC-1α pathways, thereby not only enhancing mitochondrial biogenesis and exercise endurance but also improving glucose metabolism.
to play a crucial role in regulating lifespan in nematodes and Drosophila species, thus contributing to the wide recognition of SIRT1 as a metabolic pathway of interest [39]. Adding to this was a finding that resveratrol induces the expression and activation of SIRT1 and thus serves as an exercise mimic [40]. Despite having been initially described as a direct activator of SIRT1, resveratrol has subsequently been shown to activate SIRT1 indirectly via AMPK by increasing the level of its substrate NAD⁺ [41, 42]. However, resveratrol is shown to activate skeletal muscle SIRT1 and enhance PGC-1α activity, thus activating ERRα, ERRγ, and PPARδ, all in one stroke—a genomic boost that entails collective induction of genes implicated in controlling mitochondrial biogenesis, fatty acid transport, and oxidative metabolism. Thus, while relatively weak in efficacy, resveratrol is still shown to be capable of providing exercise-mimicking benefits (e.g., protection against diet-induced obesity) [40]. Of note, recently, data from RCTs showed that resveratrol stimulated SIRT1 in humans and contributed to the treatment of excess weight and its comorbidities [43]. However, the number of studies conducted to date is too few to draw any definitive conclusions regarding the effects of resveratrol on weight loss in humans. Thus, further research is required to investigate it, with a focus on its dose, efficacy, and chronic exposure effects [43]. Further evidence for the exercise-mimicking benefits of activating SIRT1 has recently been provided by animal studies using other NAD⁺-boosting compounds, e.g., nicotinamide riboside (NR), a natural NAD⁺ precursor, and PARP1 inhibitors, both of which are shown to elevate mitochondrial oxidative metabolism and protect against metabolic diet-induced abnormalities [44, 45] (Table 1). Of particular note here is a research finding that the adiponectin/AdipoR1 pathway activates SIRT1 by elevating the NAD⁺/NADH ratio in skeletal muscles and that SIRT1, thus activated, accelerates deacetylation of PGC-1α [6]. More specifically, these processes are shown to involve NAD⁺-dependent deacetylation via SIRT1 of 13 lysine residues in PGC-1α leading to increased expression of mitochondria-related genes. Very interestingly, deacetylation of PGC-1α is also shown to be mediated by AMPK and SIRT1 associated with locomotor stimulation [41] (Fig. 1).

### The Adiponectin/AdipoR1 Pathway Activates Exercise Signaling

The quantity of activated PGC-1α has been shown to be decreased to about one-fourth in muscle-specific AdipoR1-deficient mice, accompanied by decreases in mitochondrial mass and function as well as in proportion of type I fibers, thus resulting in decreased exercise endurance, impaired glucose tolerance, and insulin resistance [6]. It was also shown that two weeks of exercise therapy led to complete reversal of not only skeletal muscle mitochondrial mass and function but impaired glucose tolerance and insulin resistance in muscle-specific AdipoR1-deficient mice [6]. It should be extremely interesting to note that the various agents used to recover Ca²⁺ signaling and AMPK/SIRT1 activity led to only partial reversal of the phenotypes associated with muscle-specific AdipoR1-deficient mice, suggesting that it is crucial to ensure that Ca²⁺ signaling and the AMPK/SIRT pathways are activated simultaneously as in exercise (Fig. 1).

#### Potential of AdipoR Activators as Exercise Mimetics

In 2013, AdipoRon (Adiponectin Receptor Agonist) has been identified as an AdipoR activator [46]. Made available as an orally administered, small-molecule compound, AdipoRon is shown in vivo to activate AMPK/SIRT1 via skeletal muscle AdipoR1, thus enhancing mitochondrial function and improving muscular endurance [46]. It has also become clear that AdipoRon not only exerts antidiabetic effects via AdipoR on the liver, skeletal muscle and adipose tissue but improves life expectancy [46, 47]. In order to ensure that AdipoRon will be made available for clinical use as an exercise mimic and as a therapeutic agent for lifestyle-related diseases, however, it remains extremely crucial to examine whether or not it may indeed act on human AdipoR in vivo. Only recently have AdipoR-humanized mice been generated to validate the effects of AdipoRon on human AdipoR [48]; this entailed, first, generating muscle-specific human AdipoR1 transgenic mice as a gain-of-function system, which demonstrated that the expression of mitochondria-related and oxidative-stress-detrifying genes are increased in skeletal muscles, thus leading to improvements in insulin resistance and muscular endurance. Furthermore, generated by crossing AdipoR1 R2 double-knockout mice with muscle-specific human AdipoR1 transgenic mice, AdipoR-humanized mice have proved to be instrumental in demonstrating that AdipoRon confers favorable benefits on skeletal muscles through human AdipoR and enhances insulin sensitivity and exercise endurance in AdipoR-humanized mice—a finding that human AdipoR1 expressed in skeletal muscles could represent an exercise mimic and that AdipoRon could deliver its benefits via human AdipoR1 [48] (Table 1).
Crystal Structural Features of AdipoR

The available crystal structural information on AdipoR could serve as a powerful tool in optimizing AdipoR activators for clinical use. The elucidation in 2015 of the crystal structures of AdipoR led to the finding that AdipoR has a novel structure and function distinct from those of GPCRs [49]. It is only recently that AdipoR1 has been further structurally characterized [50] as taking both closed and open forms, where the cavity in the transmembrane domain of the latter is shown to be wide open, particularly with the intercellular ends of helix V shifted by 11 Å. Moreover, it was found that oleic acid is present in the transmembrane cavities of AdipoR1 and AdipoR2, which is thought likely to be a hydrolytic product of AdipoR. It is expected that further analyses of the substrate specificities versus conformational changes of AdipoR will elucidate the AdipoR-mediated mechanisms of glucose/lipid metabolism in greater detail.

Perspectives

Elucidation of the crystal structure of AdipoR is expected not only to unravel the signal transduction mechanisms in AdipoR as a novel seven-transmembrane receptor but to accelerate the development of AdipoR activators and, by extension, exercise mimetics. It is expected that the development of the world’s first AdipoR activator is further accelerated in the forthcoming years to help not only establish an effective preventive and therapeutic approach to lifestyle-related diseases whose underlying pathology is obesity, but realize healthy longevity in humans.

Author Contributions

M.I., M.O.-I., T.K., and T.Yamauchi wrote the manuscript. All authors reviewed the manuscript.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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