REVIEW ARTICLE

Metabolic Adaptations to Exercise Training

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Abstract

The health benefits of exercise have attracted substantial attention, because regular exercise can strengthen muscles and improve endurance. Physical activity is an integral part of an overall healthy lifestyle, which helps protect against chronic diseases, such as obesity, insulin resistance and type 2 diabetes. In consideration of the differences in duration, intensity, and type of activity of exercise, it is likely to involve different signaling pathways and bring different benefits in different tissues. Here we review our growing knowledge of exercise training adaptations and regulation in cellular processes related to energy metabolism, aging and autophagy, and many important findings remain to be discovered.

Keywords Exercise · Energy metabolism · Aging · Epigenetic · Autophagy · Gut microbiota

Introduction

Sedentary lifestyles increase all causes of multiple adverse health outcomes and regular exercise is necessary for physical fitness and good health. Exercise training reduces the risk of heart disease, cancer, high blood pressure, diabetes and other diseases. It also improves your appearance and delay the aging process. Moreover, physiological systems possess acute and chronic adaptations to exercise dependent on volume and intensity [34, 42]. Energy for acute exercise is derived from a small amount of ATP and CP stored in muscle cells. Once the ATP-CP store is exhausted, the muscles resort to the rapid breakdown of stored glycogen-glucose for ATP regeneration via the glycolytic pathway. Strenuous exercise could result in lactic acid accumulation, decrease of mucle calcium-binding capacity, increase of heart rate/cardiac output and muscle damage [46]. Increase of oxygen consumption induced by acute exercise leads to increase in the production of reactive oxygen and nitrogen species (RONS) that is associated with muscle fatigue or damage [3]. In addition, A study by Petriz et al. [42] with proteomic analysis showed that protein carbonylation and enzymes related to energy metabolism were significantly reduced in the soleus muscle after the acute bout. Aerobic exercise elicits many adaptations in the involved skeletal muscles and in the metabolic and cardiorespiratory systems. Endurance training leads to an increase in left ventricular muscle mass and dilatation, an increase of blood flow to active muscles, an increase of VO_{2peak}, aerobic capacity and extract oxygen capacity [10, 24]. Additionally, proteomic analysis shows that regular exercise increases mitochondrial content and enzymes involved in oxidative phosphorylation and fatty acid utilization [10, 30] and reduces glycolytic proteins (e.g., cytoplasmic alpha-enolase) and creatine kinase carbonylation in muscle [42]. However, despite numerous research efforts in this field, the underlying molecular mechanisms of exercise-induced benefits for organisms are still not fully understood. In the past 10 years, we have been mainly investigated the molecular mechanisms of exercise- induced insulin sensitivity in major insulin-target tissues, predominantly skeletal muscle. This review summarized the current knowledge of exercise metabolism from our laboratory and others. We aim to provide mechanistic insight for basic studies and clinical treatment of metabolic diseases such as type 2 diabetes, obesity and myopathies.

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Energy Metabolism for Skeletal Muscle During Exercise

Skeletal muscle, a dynamic tissue with considerable plasticity, is able to rapidly adapt to drastic changes in energy demands during exercise, through fine-tuning of the balance between catabolic and anabolic processes. Glucose and lipid are the mainly fuels that support contracting skeletal muscle during continuous exercise lasting longer than several minutes, while amino acids have only a minor contribution [18, 59]. Exercise rapidly increases glucose uptake to sustain the energy expenditure by increased ATP turnover in an intensity-dependent manner in contracting skeletal muscle [33]. Compared to the limited stores of carbohydrate, endogenous lipid stores represent a potentially unlimited and plentiful fuel for skeletal muscle metabolism during aerobic exercise [22]. Given that glucose and lipid are the mainly fuels for energy demand, better understanding their regulatory mechanisms of metabolism during exercise is particularly important. Exercise plays pleiotropic roles in multiple organ systems. Therefore, it is unlikely that a single targeting pathway could recapitulate the pleiotropic effects of exercise. As promising candidates, AMP-activated protein kinase (AMPK) and mechanistic target of rapamycin (mTOR) are used to state the beneficial responses of exercise [11, 28, 37, 41, 45, 52]. And we summarized the signaling pathways between AMPK, mTOR and Sestrins in glucose and lipid metabolism after exercise in Fig. 1.

Metabolic Regulation During Exercise: The Role of AMPK

AMPK, a heterotrimeric complex, comprises a catalytic subunit (α), a scaffolding subunit (β) and a regulatory subunit (γ). As we know, AMPK is activated by rising AMP/ATP and ADP/ATP ratios under conditions of energy stress, such as nutrient deprivation and physical exercise [27]. Aerobic exercise and acute exercise both activate AMPK in the skeletal muscle of both human and rodents [43]. Once activated, AMPK regulates multiple signaling pathways, and then affects the glucose and lipid metabolism. GLUT4, a key glucose transporter isoform, is responsible for glucose transport in skeletal muscle following insulin or exercise stimulation [41]. Previous evidences indicate that aerobic exercise enhanced glucose oxidation and glucose uptake through increasing GLUT4 transcription in skeletal muscle [11]. We observed that GLUT4 gene and protein expression significantly increased after aerobic exercise in wild type mice, while decreased in AMPKα2$^{-/-}$ mice [37]. Our finding showed that the
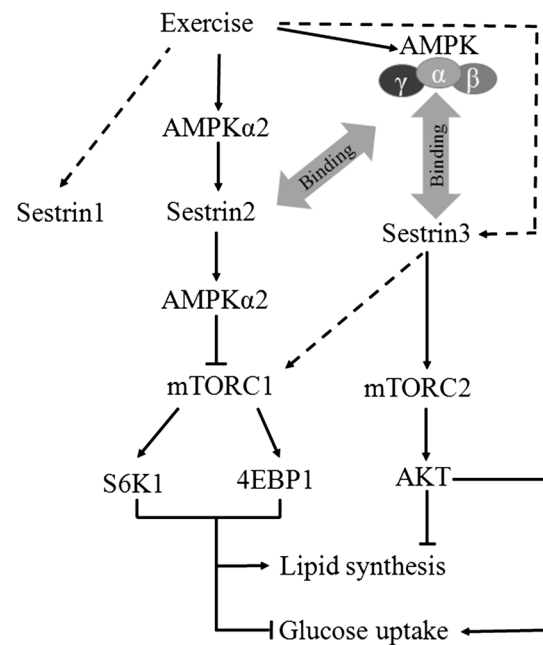

Fig. 1 The proposed signaling pathways of AMPK, mTOR and Sestrins in glucose and lipid metabolism after exercise. *AMPK* adenosine monophosphate-activated protein kinase, *mTOR* mechanistic target of rapamycin, *S6K1* phosphorylation of p70 S6 kinase, *4EBP1* eukaryotic translation initiation factor 4E-binding protein 1, *AKT* protein kinase B

exercise-related benefits on GLUT4 was completely reversed when AMPKα2 is knocked out, suggesting that exercise promoted GLUT4 transcription in an AMPKα2-dependent manner in mouse skeletal muscle [37]. And we also found that exercise reversed high-fat-diet (HFD)-induced insulin resistance and decreased intramyocellular lipid accumulation through AMPK signaling [28]. Moreover, acute activation of AMPK increased glucose transport and fatty acid oxidation, but decreased glycogen synthase activity and protein synthesis [22]. Additionally, activation of AMPK by AICAR, a pharmacological activator of AMPK, increased insulin sensitivity in skeletal muscles thereby increasing glucose transport [48]. As mentioned above, AMPK is necessary for glucose and lipid metabolism in exercising skeletal muscle, and may be used as a possible therapeutic target for the treatment of type 2 diabetes and obesity.

Metabolic Regulation During Exercise: The Role of mTOR

mTOR, a highly conserved serine/threonine kinase, controls a diverse array of physiological processes including cell growth, cell survival, cell differentiation, immune function, diabetes, and aging [55]. mTOR complex 1 (mTORC1) and complex 2 (mTORC2), two distinct complexes of mTOR, are

characterized by the presence of raptor and rictor, and exert different functions, respectively [20]. As a master controller of anabolic metabolism, mTORC1 has been shown to promote protein synthesis mainly through phosphorylation of p70 S6 kinase (S6K1) and eukaryotic translation initiation factor 4E-binding protein 1 (4EBP1), and increase lipid synthesis through SREBP1/2 [23]. Unlike mTORC1, the function and regulation mechanism of mTORC2 are less understood. Here we focus on the regulation of mTOR to glucose and lipid metabolism processes. A regulatory feedback loop exists between mTORC1 and mTORC2, and also between them and glucose/lipid content. The postprandial-induced insulin activates Akt through mTORC2 [49]. mTORC2 increases glycogen synthesis, whereas it decreases gluconeogenesis through AKT [16]. mTORC1 is indirectly activated by Akt through phosphorylating TSC1/2, which then phosphorylates IRS-1, leading a negative feedback regulation of the insulin signaling. mTORC1 promotes lipogenesis and inhibits lipolysis and β-oxidation by SREBP [12, 28, 44]. Consistent with those findings, our data showed that downregulation of mTOR/S6K1 signaling inhibited SREBP-1c cleavage, and then increased the lipogenesis in C2C12 myotubes [28]. Moreover, we found that knockdown of S6K1 increased the insulin-dependent pAkt-S473 and significantly decreased pIRS1-S636/639; palmitate-induced activation of Akt resulted in concomitant increase in mTORC1 activity in C2C12 myotubes [28]. As reported previously [45, 52], we also found that AMPK/mTOR/S6K1 signaling axis exerted an important role in mediating exercise-induced insulin sensitization and fatty acid oxidation in the skeletal muscle of C57BL/6 mice [28].

Metabolic Regulation During Exercise: The Role of Sestrins

Sestrins are highly conserved stress-inducible proteins, including Sesn1, Sesn2 and Sesn3 in mammals [7]. Sestrins knock-out mice display many metabolic dysfunctions as follows: (1) Sesn2 deficiency aggravates obesity-induced mTORC1-S6K activation, glucose intolerance, insulin resistance and hepatosteatosis in liver and adipose tissue; (2) Spontaneous insulin resistance was observed in Sesn2$^{-/-}$/Sesn3$^{-/-}$ (DKO) mice [25]. Those abnormal metabolic phenotypes caused by Sestrins loss were reversed after AMPK activation. These findings indicate that both Sesn2 and Sesn3 are necessary for blood glucose and lipid homeostasis and Sestrins regulate the metabolic homeostasis through inhibition of mTORC1 in an AMPK-dependent manner. Considering this finding, compound C pharmacological or shRNA-mediated inhibition of AMPK aggravated the inhibition of mTORC1 by Sestrins [6], confirming that AMPK is the key downstream molecule of Sestrins. However, a recent study showed that Sestrins suppressed

mTORC1 in AMPK-null mouse embryonic fibroblasts [39], suggesting that AMPK may not be the only target of Sestrins in the mTORC1 pathway. Our data showed that AMPK binds to Sesn2/Sesn3, and mediates the effect of exercise to increase insulin-sensitivity [39]. In addition, we reported that Sesn2 induced autophagy and attenuated insulin resistance caused by palmitate through activating the AMPK signaling in C2C12 myotubes. These findings indicated that Sestrins/AMPK/mTOR is a crucial signaling pathway in regulating glucose and lipid metabolism, and more efforts are warranted to explore the exact role of Sestrins in AMPK signaling, especially in exercise condition.

Potential Mechanisms of Exercise-Induced Metabolic Health

Protecting Against Aging by Exercise

Aging is associated with a gradual deterioration of daily living activities and physical function, usually accompanied by increased occurrence of muscular, cognition and metabolic disorders, such as sarcopenia, Alzheimer's disease and type 2 diabetes mellitus [14]. To date, numerous researches have demonstrated that oxidative capacity, mitochondria, mass, strength, and power of skeletal muscle decline in the aging process [14, 17, 21]. A study by Yu et al. showed that resistance exercise countered the declines in muscle mass, strength, and power in elderly adults [56]. Because of limited active exercises in elderly, passive exercises tend to play a complementary role in maintaining the elderly's physical and mental statuses. Continuous pulsed electromagnetic field (EMF) exposure for 60 days partially improved cognitive and psychomotor activity in senescent rats [51]. In addition, recent evidence indicates that exercise training rescues aging-induced mitochondrial fragmentation in skeletal muscle by suppressing mitochondrial fission protein expression in a PGC-1α dependent manner [17]. Moreover, sirtuins, AMPK, and PARPs are reported as pro-longevity and health span-related factors, while mTOR-S6K and ERK seem to negatively affect health span and to be associated DNA damage, a marker of cellular aging [50]. Our previous study demonstrated that mTOR and its upstream brain-derived neurotrophic factor (BDNF)/phosphatidylinositide 3-kinase (PI3 K)/protein kinase B (Akt) signaling was decreased in hippocampus of mice with age-related cognitive dysfunction [53]. Interestingly, we recently found that pAMPK-T172, Sesn1 and Sesn2 proteins were significantly decreased in sarcopenia C57BL/6 mice, accompanied by skeletal muscle mitochondria dysfunction including abnormal fusion/fission, biogenesis and mitophagy. Six-week aerobic exercise could significantly attenuate the above-mentioned dysfunctions. We used siRNA to down-regulation Sesn2 in C2C12

cells and observed mitochondria dysfunction and reactive oxygen species (ROS) accumulation, which were partially reversed after AICAR treatment, an activator of AMPK (unpublished data). Therefore, our finding indicates that exercise improves or ameliorates aging-induced sarcopenia by mediating the Sesn2/AMPK pathway. Sesn2 knock-out mice are being used for our further study to explore the exact role of Sesn2 in aging-associated exercise adaptation. These findings reinforce more studies are needed to explore the molecule mechanism of exercise in delaying or protecting organism against aging.

Regulation of Epigenetics During Exercise

Epigenetics has been defined as all the meiotically and mitotically inherited changes in gene expression that are not encoded in the DNA sequence itself. Epigenetic modifications include DNA methylation, histone modification and non-coding RNA [5]. The epigenome is influenced by environmental factors (e.g., drugs, diet, exercise and stress) and the aging process throughout life [35]. Emerging evidences demonstrated that the effects of epigenetic modifications on health and disease are extensive and aberrant epigenetic modifications could be experienced by future generations through transgenerational epigenetic inheritance [35]. Numerous studies from us and others have already shown that exercise modified expression of many genes associated with skeletal muscle performance, glucose and lipid metabolism, mitochondrial function as well as cognitive function [17, 28, 33, 37, 53]. Previous data suggested that three-quarters of the identified genes had low DNA methylation in skeletal muscle, and the majority of the genes had high DNA methylation in adipose tissue after regular exercise [36, 47]. Our results showed that paternal treadmill exercise improved the spatial learning and memory capability of male pups, which was accompanied by increasing BDNF expression in hippocampus [54]. In addition, we recently found that exercise regulated GLUT4 transcription and fatty acid β-oxidation through histone deacetylase (HDAC) 4 and 5, respectively [37, 57]. In addition, we also explored the regulation and underlying mechanism of exercise to microRNA, a non-coding RNA. We found that miR-206 significantly increased in soleus of mice following 6-week aerobic exercise. Furthermore, after miR-206 mimic treatment, HDAC4 was decreased in C2C12 cells, accompanied by increased GLUT4 transcription and glucose uptake (unpublished data). Our results indicated that aerobic exercise-induced upregulation of skeletal muscle glucose metabolism may be mediated by HDAC4 and may be closely associated with miR-206. These findings demonstrated that regular exercise induced changes of gene expression or transcription, such genome-wide epigenetic modifications may enable scientists

to developing new epigenetic drugs that could mimic the beneficial effects of exercise.

Regulation of Autophagy During Exercise

Autophagy is an evolutionarily conserved lysosomal catabolic pathway and an intracellular recycling system that eliminates intracellular defective protein and malfunctioned organelles [38]. Autophagy can be affected by multiple types of cellular environment factors, such as nutrition deprivation, hypoxia and anoxia, or endoplasmic reticulum stress [1]. Decline of autophagy causes abnormal accumulation of damaged mitochondria and ROS, giving rise to neurodegenerative disease [58]. Likewise, our preliminary data showed that autophagy activation decreased after 3-month, 12-month and 20-month aging-time, which was associated with cognitive dysfunction of mice [53]. In additional, defects in autophagy potentially results in the disorders of whole-body glucose and lipid metabolism and the development of metabolic diseases [4]. Consistent with this, our laboratory found that overexpression Sesn2 increased autophagy activation through the AMPK signaling, and then relieved palmitate-induced insulin resistance in C2C12 myotubes. The above phenomenon was eliminated after 3-MA intervention, an inhibitor of autophagy [26]. Moreover, we also found that autophagy regulated muscle glucose homeostasis and increased insulin sensitivity in response to exercise training, which was mediated by binding AMPK and Sestrins [29]. Findings from us and others indicate that a potential link between exercise and autophagy has been related to AMPK activation. We have shown that a single-bout exercise is sufficient to turn on autophagy in skeletal muscles of mice, which is closely associated with AMPK activation. We used AMPKα2 knockout mice and found that loss of AMPKα2 impaired stimulation of autophagy during exercise, which suggested that AMPK activation was necessary for exercise-induced autophagic response in skeletal muscle. Furthermore, this study showed increased or decreased glucose uptake was associated with activation or inhibition of autophagy in C2C12 myotubes, respectively. Although numerous studies focus on autophagy, its molecular regulation mechanism is largely unknown, especially in physical exercise condition.

Modifying of Gut Microbiota During Exercise

It is generally accepted that there are trillions of microorganisms existing in our intestines, and their metabolic products affect intestinal health. The function of gut microbiota is obtained and better known via germ-free or specific pathogen-free animals used by a lot of researchers [2]. Gut microbiota provides nutrients, regulates the intestinal mucosa/epithelial development, and affects the immune

system and homeostasis, which is deserved as an endocrine organ [32]. Gut microbiota dysbiosis can result in several diseases, such as cancer [9], inflammatory disorders [15], metabolic diseases including obesity and diabetes, and cardiovascular diseases [40]. As the two important modifiable factors, diet and exercise significantly affect gut microbiota. Although the interaction between diet and microbiota has been studied widely, the relation between exercise and the microbiota is still in its infancy. Recent study suggested that physical exercise increased the number of beneficial microbial species and diversity [32], and then maintain glucose and lipid homeostasis [40]. A study showed that voluntary running exercise increased butyrate concentration and diameter of cecum, protecting against colon cancer [31]. In addition, exercise reversed HFD-induced obesity, promoted to produce a microbial composition similar to lean mice, reduced inflammatory infiltration, and protected the intestine morphology/integrity [8, 13]. Similarly, we found that fat mass, LPS in serum and TNF-α expression increased after HFD treatment in C57BL/6 mice, which are all reversed by 6-week exercise and/or butyrate administration. Moreover, our data show that probiotics significantly increases after exercise in feces by intestinal flora analysis (unpublished data). Interestingly, microbiota profiles also affect exercise performance and which may depend on glutathione peroxidase and catalase activity [19]. Therefore, interaction of microbiota-exercise may be bidirectional and an optimal microbial makeup could promote exercise performance. Modifying the microbiota as a supplement would be used to enhance athletic performance.

Conclusions

Metabolic adaptation to exercise training is complicated. That differs in duration, intensity, and type of exercise. And it may involve different signaling pathways and exert multiple benefits. Given the benefits of exercise on numerous tissues, now, more than ever, we need to keep the momentum of exercise research going in order to improve our health and wellness.

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