High-intensity interval training enhances oxidative capacity and substrate availability in skeletal muscle

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Abstract

High-intensity interval training (HIIT) consists of repeated short bursts of high-intensity exercise and rest. Here we review recent work focusing on the metabolic adaptations to HIIT, especially in oxidative capacity and substrate availability in skeletal muscle. In this review, HIIT is defined as chronic training, for at least 2 weeks, involving repeated short-duration high-intensity exercise at >85% VO2 max, followed by complete rest or active rest, for any given duration of exercise and rest. First, we describe the effects of HIIT on muscle substrate oxidative metabolism, specifically in terms of mitochondria and substrate transporters. HIIT changes muscle mitochondrial content, function and dynamics. HIIT increases the protein content of transporters of glucose, lactate and fatty acids in skeletal muscle. These adaptations of mitochondria and transporter proteins improve oxidative capacity and substrate availability in skeletal muscle. Second, we introduce a potential mechanism of HIIT-induced adaptations in skeletal muscle, focusing on mitochondrial biogenesis. It is well known that a mechanism of mitochondrial biogenesis involves PGC-1alpha protein and its upstream signaling pathways including Ca2+/calmodulin-dependent protein kinase, AMP-activated protein kinase and mitogen-activated protein kinase p38. Given that mitochondrial biogenesis occurs in an exercise-intensity-dependent manner, mobilization of fast-twitch fibers and lactate accumulation are important. Finally, we discuss the future direction of HIIT research, involving systems biology approaches such as omics technologies and mathematical modeling, which may overcome current limitations and accelerate our understanding of mechanisms of HIIT-induced adaptations.

Keywords: high-intensity interval training, skeletal muscle, mitochondria, substrate transporter

Introduction

High-intensity interval training (HIIT) is a form of exercise training that consists of repeated short high-intensity exercise and rest (complete rest or recovery with low-intensity exercise). HIIT was originally used as a type of “sprint training” for enhancing sprint performance and is strongly associated with anaerobic metabolism, i.e., breakdown of high energy phosphates (ATP and phosphocreatine (PCr)) and glycogen (glycolysis and glycogenolysis)5). Indeed HIIT enhanced the capacity for PCr depletion5 and glycolytic enzyme activities (e.g., phosphofructokinase)5,6 in skeletal muscle. However, many recent studies have demonstrated that HIIT also enhances substrate oxidative capacity, which is associated with mitochondrial enzyme activity and substrate transporters5. This evidence is in fact not new; several classic studies showed similar results using animal models.

In a milestone paper of sport science, Holloszy et al. revealed increases in the activities of the mitochondrial enzymes cytochrome oxidase (COX) and succinate dehydrogenase (SDH) in skeletal muscle after exercise training of rats6. This work is cited frequently as showing that “endurance” exercise training increases mitochondrial enzyme activity. However, the actual exercise program in the study included HIIT. In addition, elegant work by Dudley et al. demonstrated that increases in cytochrome c concentration, which reflects mitochondrial content in cells, occurred in an exercise-intensity-dependent manner in rat hindlimb muscle7. Thus, HIIT-induced adaptations affect aerobic exercise capacity and are associated with mitochondrial enzyme activities and protein content. It is well known that Emil Zatopek, a Czechoslovak long-distance runner and winner of three gold medals, including the marathon at the Helsinki Olympic Games in 1952, frequently and favorably undertook HIIT.

Recent studies suggest that HIIT provides comparable effects to traditional continuous endurance training on muscle oxidative capacity and substrate availability8,9. Because ‘lack of time’ remains one of the most commonly cited barriers to regular exercise participation10,11, exercise scientists in academia as well as trainers and coaches...
in sport have become keenly interested in new knowledge and understanding about HIIT\textsuperscript{12}. Here we review recent works focusing on metabolic adaptations to HIIT, especially muscle oxidative capacity and substrate availability. In this review, we define HIIT as chronic training (for at least 2 weeks) with repeated exercise at \( >85\% \text{VO}_2\max \) (or peak) followed by rest, for any given duration of exercise and rest. Resistance type training is not included in HIIT in this review. First, we describe the effects of HIIT on muscle substrate oxidative metabolism, specifically mitochondria and substrate transporters. Second, we introduce one potential mechanism of HIIT-induced adaptations in skeletal muscle, mitochondrial biogenesis. Last, we introduce future directions of HIIT research, associated with systems biology approaches such as omics technologies and mathematical modeling.

Effects of HIIT on substrate metabolism in skeletal muscle

Mitochondria and substrate transporters play important roles in muscle substrate oxidative metabolism. Mitochondria are the central organelle for oxidation of substrates (glucose, fatty acid and lactate) for ATP production via tricarboxylic acid cycle (TCA cycle) and electron transport chain to maintain homeostatic levels of ATP. Transporters are proteins in membranes or pooled in the cytosol that have critical roles in specific substrate transport regulation in both plasmalemmal and mitochondrial membranes. Here we focus on glucose, lactate and fatty acid transporters. Fig. 1 shows a simple scheme of substrate oxidative metabolism in skeletal muscle, involving mitochondria and relevant transporters.

Mitochondria. We consider mitochondrial adaptations to exercise in terms of three aspects: 1) mitochondrial content and volume; 2) functions; and 3) dynamics (Fig. 2).

1) Mitochondrial content and volume

By “mitochondrial content”, we broadly mean the number of mitochondria and their total volume in cells. Many studies have examined the maximal activity and protein level of mitochondrial enzymes as indicators of mitochondrial content and volume, for example citrate synthase (CS), COX and SDH measured by biochemical assays. Mitochondrial DNA and other indices are also considered good markers of mitochondrial content; but which is the best marker is still controversial\textsuperscript{13}).

HIIT increases the maximal activity of CS and COX, which reflects increases in skeletal muscle mitochondrial content, in mice\textsuperscript{14,15}, rats\textsuperscript{16,17}, horses\textsuperscript{18} and humans\textsuperscript{19-23}. Interestingly, the increases in these activities and protein levels following HIIT are comparable to those after continuous endurance exercise training, even though the total energy consumption during exercise was lower in HIIT\textsuperscript{8,9}. Therefore, HIIT makes it possible to increase

Fig. 1 Simple scheme of substrate oxidative metabolism, particularly considering mitochondria and transporters in skeletal muscle. HIIT increased mitochondrial biogenesis and transporter proteins (FAT/CD36, FABPpm, GLUT4, MCT1 and MCT4). Long-chain fatty acid, LCFA; triacylglycerol, TAG; fatty acid translocase/CD36, FAT/CD36; fatty acid binding protein, FABPpm; glucose transporter 4, GLUT4; monocarboxylate transporter, MCT.
JPFSM: HIIT enhances muscle oxidative capacity and substrate availability

HIIT enhances muscle oxidative capacity and substrate availability with much shorter exercise duration than traditional endurance training. Because the mitochondrial volume is related to insulin sensitivity, muscle atrophy, and exercise performance, HIIT is a useful method for the improvement of oxidative capacity that prevents muscle disorders and enhances exercise performance.

Although HIIT consists of high-intensity exercise and rest, the specific patterns of exercise varied widely in previous studies. The shortest exercise duration was 20 s and the longest 4 min. This suggests that the duration of exercise and rest do not matter for increases in mitochondrial content if the intensity is >85% VO2 max. In fact, we reported that a 3-wk HIIT of repeated 1 min high-intensity exercise with long (19 min) rest increased CS activity in mouse skeletal muscle. Moreover, mitochondrial quantitative adaptation depended on exercise intensity, but not on the exercise pattern. Overall, mitochondrial content is increased by HIIT, leading to an improvement of muscle aerobic capacity that is modulated more by exercise intensity than the durations of exercise and/or rest.

2) Mitochondrial functions

It is more difficult to investigate mitochondrial functions compared with enzyme activities that reflect the mitochondrial content. There are some methods to assess mitochondrial function in which a general method is mitochondrial isolation from tissues. Using this method, we investigated the effects of HIIT on the palmitate oxidation rate in isolated mitochondria from skeletal muscles as one mitochondrial function. We used rats that performed HIIT for 5 days per week for 4 weeks. Isolated mitochondrial palmitate oxidation rates in rat red and white skeletal muscles were higher in the HIIT group than in the control group (Fig. 3). In other words, HIIT increased palmitate oxidation rates per mitochondrial protein content. These data were supported by another study showing that HIIT is more effective than continuous submaximal exercise training for increasing rates of fatty acid oxidation in isolated mitochondria in rat muscles. Therefore, these studies using the mitochondrial isolation method suggest that HIIT improved mitochondrial function per mitochondrial protein level regardless of mitochondrial quantitative changes.

However, mitochondrial isolation may alter normal mitochondrial morphology, possibly impairing mitochondrial functional properties. To resolve this issue, the method of permeabilized fibers was developed. Using this approach, Ramos et al. found that HIIT influenced several substrate respiration rates in different muscle types in rats. Interestingly, in a human study, the maximal mitochondrial respiration of specific substrates in permeabilized muscle fibers increased significantly only after all-out exercise interval training without changes in mitochondrial content. This is consistent with another study showing that mitochondrial respiration capacity improved with aerobic capacity independent of the mitochondrial content in human skeletal muscle. These reports suggest there is dissociation between training-induced changes in mitochondrial function and content. We have to consider not only mitochondrial quantities but also their functional adaptations to HIIT.

3) Mitochondrial dynamics

Mitochondrial dynamics -fusion and fission- are known...
to be important for mitochondrial quality control. The proteins involved in fusion are mitofusin proteins (MFN1 and 2) and optic atrophy 1 (OPA1), and the proteins involved in fission are fission protein 1 (FIS1) and dynamin related protein 1 (DRP1). It is of interest to clarify the effects of HIIT on these factors; however, only a few studies have examined this issue. Perry et al. reported that HIIT (10 bouts of 4 min at 90% VO\textsubscript{2} peak exercise and 2 min rest) increased the protein content of MFN1, FIS1 and DRP1, but not MFN2, in humans\textsuperscript{33}). Another group showed that MFN2 increased after HIIT in patients with type II diabetes who usually have reduced mitochondrial fusion and elongation\textsuperscript{34}). These data suggested that HIIT may influence mitochondrial dynamics, via increases in mitochondrial fusion and fission proteins. However, whether changes in fusion/fission proteins due to HIIT alter mitochondrial morphology is still unknown. Recently, our group also reported increases in MFN1, MFN2, and OPA1 in rat skeletal muscle after 4 weeks of resistance training\textsuperscript{35}). Increased mitochondrial fusion proteins were also observed after 7 days of chronic muscle contractile activity (10 Hz, 3 h/day), an endurance exercise model in rats, whereas muscle disuse through denervation for 7 days decreased these protein levels\textsuperscript{36}). Taken together, the data suggest that muscle contractile activity can alter mitochondrial dynamics, but the mechanisms remain to be elucidated.

**Transporter proteins and substrate metabolism.** Here we focus on the changes in the content of several transporter proteins after HIIT. HIIT increases glucose, lactate and fatty acid transporter proteins in skeletal muscle (Fig. 1). Because glucose, lactate and fatty acids are transported into cells by specific transporters, adaptations of such transporter proteins are important for substrate availability during exercise at the levels of muscle and the whole body.

In skeletal muscle, GLUT4 is the most important glucose transporter. The protein content regulates glucose uptake to the muscle cells\textsuperscript{37}). HIIT increased GLUT4 protein content in human\textsuperscript{34,38} and rat muscle\textsuperscript{39}). Moreover, HIIT-induced increases in GLUT4 level concomitantly improved glucose tolerance capacity in metabolic disorder patients\textsuperscript{34}). Pyruvate dehydrogenase (PDH) protein and its activity also increased after HIIT\textsuperscript{40}). At the same time, lactate accumulation and glycogen utilization during exercise was reduced with concomitant increases in muscle glycogen concentration\textsuperscript{41}). These results suggest that HIIT improved glucose availability by increases in GLUT4 protein, PDH activity and glycogen concentration in skeletal muscle.

Monocarboxylate transporters (MCT) play a critical role in lactate transport; MCT1 and MCT4 are especially important in skeletal muscle\textsuperscript{19}). MCT1 functions in lactate uptake into muscle and MCT4 functions in lactate release from muscle. Much research has shown that HIIT increased MCT1 and MCT4 protein content in rodents\textsuperscript{39}, horses\textsuperscript{19} and humans\textsuperscript{27,38}). Importantly, MCT1 can be increased after both low-intensity continuous and high-intensity training, but MCT4 increased only after high-intensity training\textsuperscript{40,41}). Therefore, exercise coupled with lactate accumulation is required for MCT4 protein adaptation. However, MCT4 is not always significantly increased even after HIIT in humans and rats\textsuperscript{42,44}). These data suggest that MCT4 protein content is not easy to increase by exercise training, and analysis of 10 human training studies suggests that changes in MCT1 protein content following training are approximately twice those of MCT4\textsuperscript{45}). HIIT up-regulates MCT1 and MCT4 protein contents and leads to the enhancement of lactate transport capacity.

HIIT can change the capacity for fat utilization in skeletal muscle via fatty acid transporters, an enzyme in mitochondrial β-oxidation and triacylglycerol regulation.
There are several fat transporter proteins, for example fatty acid translocase/CD36 (FAT/CD36), fatty acid binding protein (FABPpm), fatty acid transport protein (FATP)1 and FATP4. HIIT increased FAT/CD36 and FABPpm protein content16,27,47), but not always38). In the study in which FAT/CD36 and FABPpm levels were not changed, repeated 30 s maximal exercise was used as HIIT38). Maximal activity of β-Hydroxyacyl-CoA dehydrogenase (β-HAD), an enzyme involved in β-oxidation, was increased in horses and rats after HIIT16,48) and humans after HIIT based on 30 s maximal cycling8). These data suggest that β-HAD activity can be increased by HIIT with even short bouts of exercise (30 s), but increases in fat transporter proteins may be required for sufficient exercise duration and volume. Moreover, protein expression of adipose triglyceride lipase (ATGL) was increased in rat muscle after 5 weeks of HIIT49). At the whole body level, fat oxidation rates during submaximal exercise were increased after HIIT8,27), demonstrating that HIIT improved fatty acid availability. Interestingly, the fat utilization rate using triacylglycerol and free fatty acid during exercise at >85% VO₂ max is lower than the carbohydrate utilization rate50). This suggests that it may not be necessary to perform exercise with relatively large amounts of fat utilization for the enhancement of fat oxidative capacity in skeletal muscle. Taken together, there is no doubt that HIIT is a method for enhancing fat availability, attributing to increased fat transport, β-HAD activity and ATGL protein expression.

**Potential mechanism underlying HIIT: mitochondrial biogenesis**

To explain potential mechanisms of all HIIT-adaptations is too big a theme for this review. Therefore, we focus on one adaptation, which is mitochondrial biogenesis (Fig. 4). Please refer to the excellent recent review by Egan and Zierath broadly covering molecular mechanisms of exercise-induced muscle adaptations51).

**PGC-1alpha and HIIT.** PGC-1alpha plays a critical role in the transcriptional regulation of mitochondrial metabolic genes52), which are encoded by both nuclear and mitochondrial DNA. Indeed transfected PGC-1alpha protein

![Fig. 4 Overview of a potential mechanism of mitochondrial adaptation in skeletal muscle. Acute high-intensity interval exercise increases ADP and AMP, Ca²⁺, ROS and lactate concentrations in skeletal muscle. The intracellular environmental changes evoked by muscle contractions are triggers for activation of signal transduction including by kinases, CaMK, AMPK and p38. These activations in kinases activate PGC-1alpha protein and induce its translocation into cell nuclei. In the nucleus, PGC-1alpha works as a cotranscriptional factor, turning on transcription of mitochondrial genes. These acute responses are not sufficient to increase mitochondrial protein content; the cycle must be repeated for chronic mitochondrial adaptation (e.g., increases in mitochondrial proteins). Reactive oxygen species, ROS; Ca²⁺/calmodulin-dependent protein kinase, CaMK; AMP-activated kinase, AMPK; mitogen-activated protein kinase p38, p38.](image-url)
in skeletal muscle increased mitochondrial and substrate transporter protein expression. HIIT increased the muscle PGC-1alpha protein content in rats and humans. One of the reasons why PGC-1alpha protein level increased after HIIT is because its transcription (mRNA expression) increased after acute high-intensity exercise. It is known that PGC-1alpha regulates the transcription of PGCG-1alpha itself and translocation of PGC-1alpha to the nucleus is required for its function as a cotranscriptional factor after exercise. In fact, acute high-intensity exercise can translocate PGC-1alpha protein to the nucleus. Moreover, PGC-1alpha activation and translocation are induced by activation of several pathways, including important kinases, evoked by muscle contractions. The main kinases are Ca\textsuperscript{2+}/calmodulin-dependent protein kinase (CaMK), AMP-activated kinase (AMPK) and mitogen-activated protein kinase p38 (p38). Therefore, the regulation of muscle mitochondrial biogenesis mediated by PGC-1alpha is closely associated with how these kinases increase after acute exercise (Fig. 4).

CaMKs are activated by Ca\textsuperscript{2+}, which is released from the sarcoplasmic reticulum during muscle contraction. CaMKII and IV induce directly and indirectly PGC-1alpha protein expression and mitochondrial biogenesis. CaMKII phosphorylation was increased in an exercise-intensity-dependent manner. AMPK is activated by decreasing ATP/ADP or ATP/AMP ratios and glycogen content. AMPK activation by 5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR) stimulation acutely increased PGC-1alpha mRNA expression in rat muscle. AMPK phosphorylated PGC-1alpha, and mutation of the phosphorylation sites reduced PGC-1alpha activation and transcription of PGC-1alpha mRNA was observed after exercise. Therefore, the regulation of muscle mitochondrial biogenesis following AMPK pharmacological activation is closely associated with how these kinases increase after acute exercise (Fig. 4).

Acute high-intensity interval exercise increased p38 phosphorylation. Taken together, these data show that HIIT-induced signaling cascades involving kinases CaMK, AMPK and p38 regulate PGC-1alpha activation and translocation to the nucleus, leading to mitochondrial biogenesis in skeletal muscle.

It should be noted that a repeated and cumulative transient increase in expression of mRNAs encoding mitochondrial proteins is needed for protein adaptations (Fig. 4), though responses of signal transduction and mRNA expression to acute exercise are important for chronic mitochondrial adaptations. Perry and colleagues showed that mRNA bursts were sensitive to acute exercise, but a single high-intensity interval exercise failed to increase maximal CS activity and COX IV protein content, despite an increase in PGC-1alpha protein. In addition, chronic adaptations do not always reflect acute responses of mRNA expression in response to exercise. Therefore, there are unknown mechanisms of chronic adaptation, which cannot be explained by a response to acute exercise, to be elucidated in future studies.

**Potential roles of lactate in HIIT-induced metabolic adaptations.** Lactate is a candidate for triggering signal transduction of exercise-induced metabolic adaptations in skeletal muscle. Hashimoto et al. reported that 10 mM and 20 mM lactate increased PGC-1alpha mRNA and protein levels leading to increases in MCT1 and mitochondrial proteins in rat L6 muscle cells. This may be related to ROS-induced CaMK activation and inhibited histone deacetylase activity by lactate. We recently examined whether reduced lactate accumulation following DCA administration attenuates metabolic adaptations in vivo after HIIT. Reduced lactate concentration partially attenuated metabolic adaptations, including increases in CS activity and COX IV protein content. This study was supported by another group who showed that elevated lactate accumulation using bicarbonate administration increased the PGC-1alpha mRNA content in humans after acute high-intensity exercise. In rats, bicarbonate administration also resulted in stronger training-induced mitochondrial adaptation (CS activity). These results therefore suggest that lactate accumulation accelerates training-induced metabolic adaptations, such as mitochondrial biogenesis. However, whether lactate directly modulates the regulation is still unknown. In contrast to the positive effects of lactate, differences in lactate concentrations during interval training did not influence training-induced muscle adaptations and exercise performance. Moreover, chronic elevation of plasma lactate concentration damaged mitochondrial quality, as shown using mice having mutant mitochondrial DNA. Taken together, lactate is involved in potential mechanisms of HIIT-induced adaptation, but we need to clarify the molecular roles of lactate itself and the side-effects of excessive lactate stimulation.

**Importance of mobilization of fast-twitch fibers.** As described above, exercise intensity is important for exercise-induced muscle metabolic adaptations, especially mitochondrial biogenesis. In fact, PGC-1alpha mRNA expression and crucial kinases (CaMK, AMPK and p38) are upregulated in an exercise-intensity-dependent manner. Moreover, in human skeletal muscle, an increase in PGC-1alpha mRNA was observed after exercise at above the lactate threshold (LT), but not below the LT. Because fast-twitch fibers have been shown to possess superior glycolytic profiles in comparison with slow-twitch fibers, it has been suspected that the recruit-
ment of fast-twitch fibers is related to the accumulation of lactate. Therefore, the mobilization of fast-twitch fibers is key to inducing muscle metabolic adaptations, but it is unlikely that maximal exercise is required for the metabolic adaptations. Relatively low intensity exercise, such as interval walking, is sufficient for improvement of aero-bic capacity.

In our study, mitochondrial and fatty acid transporter protein contents were increased in mouse skeletal muscle after 4 weeks of HIIT. The training resulted in significant increases in lactate concentration in the blood (5.44 ± 0.4 mmol/l) and muscle (20.84 ± 1.34 mmol/kg wet tissue) after acute high-intensity interval exercise, but the concentration was not at a maximal level. In addition, PGC-1alpha mRNA expression after exercise was dissociated from exercise intensity when the intensity of exercise was supra-maximal. We suggest that repeated submaximal and above LT exercise with rest is efficient for HIIT-induced muscle metabolic adaptations. Optimal frequency and durations of exercise and rest must be clarified in future studies.

The measurement of blood lactate concentration after exercise is a practical and simple method for estimating the intensity of exercise and how much fast-twitch fiber is mobilized during exercise. Although it is unclear whether lactate is a direct trigger of adaptations, blood lactate concentrations can be used to estimate the activities of the kinases and PGC-1alpha mRNA expression that help to know whether the exercise intensity is sufficient or not.

Future directions of HIIT research

In this final section we introduce systems biology approaches such as omics technologies, mathematical modeling relevant to the next direction of HIIT studies. To date, HIIT-induced adaptations in skeletal muscle and the whole body were revealed by physiological, biochemical and molecular biological approaches in sports and exercise sciences. However, these approaches have limitations. First, new molecules and pathways associated with HIIT adaptations cannot be found using these classical approaches because only hypothesized specific molecules and pathways are examined. Second, it is difficult to estimate the optimal parameters for HIIT, such as intensity, duration and frequency, which maximally induce exercise adaptations. Omics technologies and mathematical modeling may remove such limitations and accelerate the understanding of mechanisms of HIIT-induced adaptations.

Omics technologies. “Omics” are methods of global and unbiased measurement and analysis. By the development of mass spectrometry and transcript sequencing, one can perform omics analysis of metabolites, RNA, proteins and more. Here we introduce a few studies using omics analysis applicable to HIIT study.

Proteomics is the method of global measurement of many proteins using mass spectrometry. Phosphoproteomics, global analysis of many phosphorylated proteins, is available for research, but not yet at a high throughput level. Changes in signaling pathways on acute exercise, for example in phosphorylated and unphosphorylated kinases, are important for muscle adaptation as described above. Hoffman et al. uncovered global phosphorylations in human muscle after prolonged exercise, including crucial kinases related to physiological adaptations. They also found new substrate proteins phosphorylated by AMPK using estimation of substrate-kinase relationships by data-driven analysis. Thus phosphoproteomic analysis after acute high-intensity interval exercise has the potential to identify new HIIT-specific kinases and pathways by comparing phosphoproteomic data after acute continuous endurance exercise.

Moreover, omic layers can be integrated using several online databases. Yugi et al. reconstructed insulin dynamics in the mammalian cell by the integration of phosphoproteomic and metabolomic data. Others performed integrated transcriptomic and phosphoproteomic data. These approaches uncovered known and unknown (new) networks and pathways without bias by connecting phosphoproteins (enzymes and protein kinases), metabolites and mRNA expression. Using these methods, we can identify HIIT-specific and endurance-specific networks and pathways in response to high-intensity exercise or endurance exercise, respectively. Collectively, “exercisome” research using omics technologies has the potential to produce unbiased and unexpected important information and generate new hypotheses.

Computational modeling and mathematical analysis.

Another relevant approach is computational modeling and mathematical analysis. A goal of exercise science is clarifying the optimal parameters of HIIT, such as intensity, duration and frequency, to induce maximal exercise adaptations. To achieve this goal, the output (e.g., mitochondrial content, transporter proteins and muscle mass) in response to divergent exercise patterns must be estimated. For the estimation of these outputs, mathematical models must be developed using plentiful data based on experiments. In fact, the model of metabolic dynamics in response to acute exercise has been developed. However, to our knowledge, molecular responses after exercise, such as signal transduction and mRNA expression, have not been examined by mathematical modeling. It is necessary to develop a model of dynamic molecular responses related to physiological adaptation to acute high-intensity interval exercise. The model of dynamic signal pathways and mRNA expression in response to insulin was developed using experimental dose-response data and time series data, for insulin. Therefore, using exercise-intensity response data and time series data during and after exercise, we can develop a model of dynamic molecular responses to acute exercise. After that, the acute model can be expanded to a chronic exercise model.
deed, using the data on intake and expenditure after acute low carbohydrate or low fat meals, a model of changes in human fat mass after chronic nutritional perturbation was developed and simulated mathematically\(^{75}\). After validation of the simulation, the study concluded that a low-fat diet is more effective for reductions in fat mass than a low-carbohydrate diet. In a similar way, if simulation and mathematical prediction of HIIT adaptations were successful, one could determine the optimal intensity, duration and frequency of HIIT to achieve the maximal outputs.

To succeed in systems biology approaches, it is necessary to organize an interdisciplinary science team. Sport scientists must communicate and research together with scientists who have different research backgrounds, for example in biology, mathematics, computer science and so on.

Conclusions

In this review, we define HIIT as chronic training involving repeated short duration exercise at >85% \(\text{VO}_2\max\) or peak and rest, whatever the durations of exercise and rest. We mainly reviewed recent work connecting muscle metabolic adaptations due to HIIT. HIIT is an excellent method to induce mitochondrial and transporter adaptations in skeletal muscle, leading to the improvement of substrate availability in muscle and the whole body. The mechanisms of HIIT-induced metabolic adaptations are mainly associated with PGC1alpha activity and important kinases (CaMK, AMPK and p38). As the future directions of HIIT research, we herein introduced omics technologies and mathematical modeling for helping to develop a better understanding of HIIT adaptation. As one can see, it is necessary to organize a divergent interdisciplinary scientific team.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this article.

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References


65) Ogasawara E, Nakada K and Hayashi J. 2010. Lactic acidemia in the pathogenesis of mice carrying mitochondrial DNA


