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Anlatısal Derleme/Narrative Review

The Effects and Role of Different Exercise Modalities on AMP-Activated Protein Kinase (AMPK) Activity: A Review of Underlying Mechanisms

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Abstract

AMP-activated protein kinase (AMPK) is a central regulator of cellular energy homeostasis and plays a critical role in metabolic adaptation to exercise. During skeletal muscle contraction, increases in the AMP/ATP ratio activate AMPK signaling pathways, promoting glucose uptake, fatty acid oxidation, and mitochondrial biogenesis while inhibiting energy-consuming anabolic processes. These molecular adaptations contribute to improved metabolic health and reduced risk of chronic diseases such as obesity, type 2 diabetes, and cardiovascular disorders. In addition, the interaction between AMPK and the mammalian target of rapamycin (mTOR) pathway represents an important mechanism explaining the distinct adaptations to endurance and resistance training. Endurance exercise predominantly activates AMPK-mediated metabolic pathways, whereas resistance training stimulates mTOR-dependent protein synthesis and muscle hypertrophy. Therefore, understanding the molecular interaction between these pathways is essential for optimizing both athletic performance and metabolic health. This review aims to summarize the structure and function of AMPK, its role in exercise metabolism, and its potential implications in the prevention and treatment of metabolic dis

Farklı Egzersiz Türlerinin AMP-Aktive Protein Kinaz (AMPK) Aktivitesi Üzerindeki Etkileri ve Rolü: Temel Mekanizmalar Üzerine Bir Derleme

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Özet

AMP ile aktive olan protein kinaz (AMPK), hücresel enerji homeostazının düzenlenmesinde merkezi bir rol oynayan önemli bir enerji sensörüdür. İskelet kası kasılması sırasında hücre içi AMP/ATP oranındaki artış AMPK sinyal yolunu aktive ederek glukoz alımını, yağ asidi oksidasyonunu ve mitokondriyal biyogenezi artırırken enerji tüketen anabolik süreçleri baskılar. Bu moleküler adaptasyonlar, metabolik sağlığın iyileşmesine katkıda bulunmakta ve obezite, tip 2 diyabet ve kardiyovasküler hastalıklar gibi kronik metabolik hastalıkların riskini azaltmaktadır. Ayrıca AMPK ile memeli rapamisin hedefi (mTOR) sinyal yolu arasındaki etkileşim, dayanıklılık ve direnç egzersizlerine verilen farklı hücresel adaptasyonların açıklanmasında önemli bir mekanizma olarak kabul edilmektedir. Dayanıklılık egzersizleri ağırlıklı olarak AMPK aracılı metabolik yolları aktive ederken, direnç egzersizleri mTOR aracılı protein sentezi ve kas hipertrofisini desteklemektedir. Bu nedenle söz konusu iki sinyal yolu arasındaki moleküler etkileşimin anlaşılması hem atletik performansın optimize edilmesi hem de metabolik sağlığın geliştirilmesi açısından büyük önem taşımaktadır. Bu derleme çalışmasının amacı AMPK'nın yapısını ve fonksiyonlarını, egzersiz metabolizması ile ilişkisini ve metabolik hastalıkların önlenmesi ve tedavisindeki potansiyel rolünü güncel literatür ışığında incelemektir.

1. INTRODUCTION

During the training process, athletes are exposed to conditioning, technical, tactical, and psychological loads. In response to these stimuli, athletes undergo adaptive processes through appropriate recovery mechanisms, resulting in both physiological and psychological adaptations. Within this framework, supercompensation, which is a fundamental principle of training adaptation, occurs when the body recovers after a training stimulus and temporarily elevates performance capacity above baseline levels (Bompa & Buzzichelli, 2019; Issurin, 2010).

Energy homeostasis is a fundamental biological process necessary for the maintenance of cellular life. Cells maintain the balance between energy production and consumption through tightly regulated signaling pathways. This balance becomes particularly critical under metabolic stress conditions such as exercise, fasting, or pathological states (Hardie, 2014; Hardie et al., 2012). AMP-activated protein kinase (AMPK) plays a key role in this process as a central intracellular energy sensor. First identified in the late twentieth century, AMPK maintains cellular energy balance by activating ATP-producing catabolic pathways while simultaneously inhibiting ATP-consuming anabolic pathways under conditions of energy deficiency (Hardie & Hawley, 2001; Hardie, 2014).

Recent studies have demonstrated that the physiological functions of AMPK extend beyond cellular energy metabolism and include the regulation of appetite, lipid metabolism, glucose uptake, and cellular growth processes (Ross et al., 2016; Hardie et al., 2012). In particular, the interaction between AMPK signaling and hypothalamic pathways that regulate energy intake and expenditure has provided important insights into the relationship between energy metabolism and feeding behavior (Hardie, 2014). Consequently, AMPK has emerged as an important therapeutic target in the prevention and management of metabolic disorders such as obesity, type 2 diabetes, and cardiovascular diseases (Richter & Ruderman, 2009; Kismiroğlu et al., 2020).

Exercise is considered one of the most potent physiological activators of AMPK. During skeletal muscle contractions, increases in the AMP/ATP ratio stimulate AMPK activation, which enhances glucose uptake and fatty acid oxidation to meet cellular energy demands (Hardie et al., 2012; Hawley et al., 2014). In addition, AMPK activation promotes the insulin-independent translocation of glucose transporter type 4 (GLUT4) to the plasma membrane, thereby increasing glucose uptake into skeletal muscle cells (Hawley, 2009; O'Neill, 2013; Richter & Hargreaves, 2013). For this reason, regular physical activity is widely recognized as playing a crucial role in preventing metabolic disorders such as insulin resistance, type 2 diabetes, and obesity (Booth et al., 2011).

At the molecular level, the interaction between AMPK and mammalian target of rapamycin complex 1 (mTORC1) represents one of the most important mechanisms explaining cellular adaptations to different exercise modalities. Under conditions of low cellular energy availability, AMPK suppresses mTORC1 activity through phosphorylation of regulatory proteins such as TSC2 and raptor, thereby limiting protein synthesis (Gwinn et al., 2008; Hardie, 2014). In contrast, resistance training activates mTORC1 signaling pathways that promote muscle protein synthesis and hypertrophy, whereas endurance exercise enhances mitochondrial biogenesis and oxidative capacity through AMPK-mediated signaling pathways (Hawley, 2009; Hughes et al., 2018). Therefore, the combined effects of resistance and endurance training, often referred to as concurrent training, remain an important topic of investigation in sports science due to the potential interference between these molecular signaling pathways (Fyfe et al., 2014; Hughes et al., 2018).

The present review aims to examine the structure and functions of AMPK, its role in exercise metabolism, natural activators of AMPK, its contribution to the prevention of metabolic diseases, and the molecular interactions between resistance and endurance training in light of current scientific literature.

2. STRUCTURE AND FUNCTION OF AMPK

AMP-activated protein kinase (AMPK) is a heterotrimeric serine/threonine kinase composed of a catalytic α subunit and two regulatory subunits, β and γ. Each subunit exists in multiple isoforms (α1, α2, β1, β2, γ1, γ2, and γ3), which can combine to form up to twelve distinct AMPK heterotrimeric complexes with tissue-specific distributions and regulatory properties (Ross et al., 2016).

AMPK functions as a central regulator of cellular energy homeostasis by sensing changes in the intracellular adenine nucleotide ratios, particularly AMP/ATP and ADP/ATP. An increase in these ratios reflects cellular energy stress and leads to activation of AMPK. Once activated, AMPK promotes ATP-generating catabolic pathways while simultaneously inhibiting ATP-consuming anabolic processes, thereby restoring cellular energy balance (Hardie et al., 2012).

In addition to its role in peripheral tissues, AMPK also participates in the regulation of whole-body energy balance through its actions in the hypothalamus, where it integrates hormonal and nutrient signals that influence food intake and energy expenditure (Hardie, 2014).

Activation of AMPK requires phosphorylation at threonine-172 (Thr172) within the activation loop of the α catalytic subunit. This phosphorylation is primarily mediated by upstream kinases such as liver kinase B1 (LKB1) and Ca^{2+}/calmodulin-dependent protein kinase kinase β (CaMKKβ). Elevated intracellular AMP levels promote AMPK activation by inducing allosteric changes, facilitating Thr172 phosphorylation by upstream kinases, and protecting the enzyme from dephosphorylation (Hawley et al., 2005; Ross et al., 2016).Both AMP and ADP contribute to the regulation of AMPK activity by binding to the γ subunit, although AMP exerts stronger allosteric activation, whereas ADP primarily stabilizes Thr172 phosphorylation and prevents its dephosphorylation (Hardie et al., 2012). AMPK activation can also be stimulated by physiological factors such as exercise as well as by several pharmacological agents and naturally occurring compounds that induce cellular energy stress (Hardie et al., 2012).

Table 1. Natural Activators of AMPK

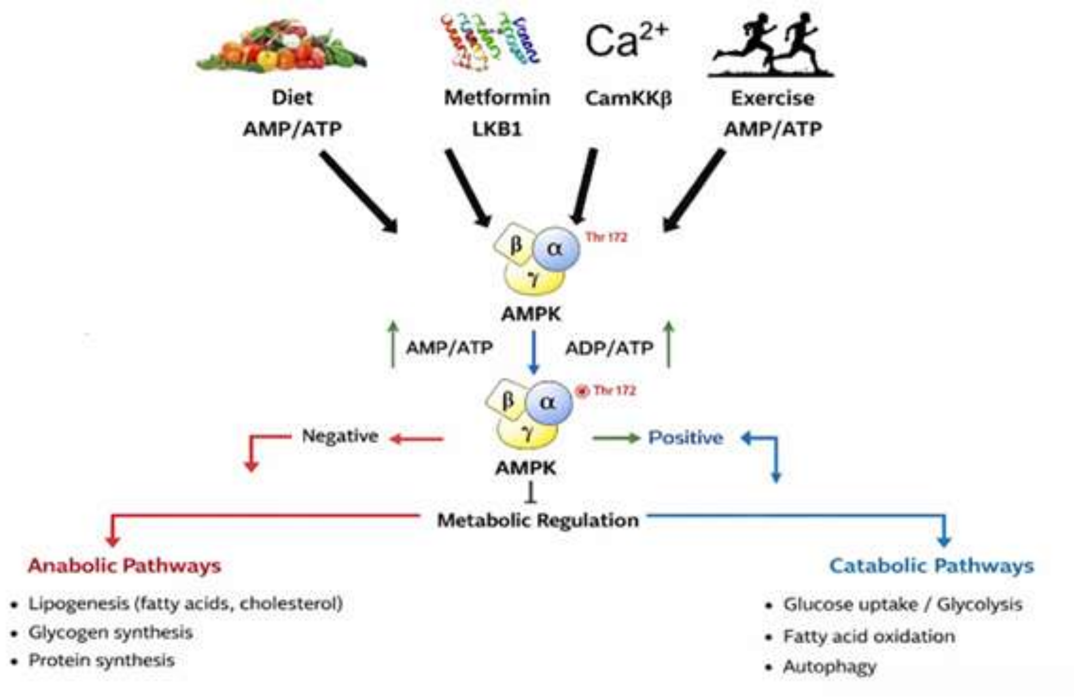
Activator	Function
Berberine	Activates AMPK; provides effects in diabetes and obesity treatment; tumor suppression.
Resveratrol	Activates AMPK; suppresses mTORC1 activity; reduces blood pressure; suppresses reactive oxygen species; promotes cardiovascular health.
Quercetin	Acts on AMPK and/or SIRT1 and supports smooth muscle health.
Salicylate	Activates AMPK; exhibits antitumorigenic and anti-inflammatory effects while reducing lipogenesis.
Curcumin	Activates AMPK, helping prevent obesity and protect cellular health.
Ginseng	Activates AMPK and mitochondrial activation.
Epigallocatechin-3-gallate	Activates AMPK, inhibiting cancer and obesity.
Aspalathus linearis (Rooibos)	Activates AMPK; regulates blood lipid levels.
Gingerol	Activates SIRT1/AMPK/PGC-1α and supports cellular repair.
MUFA	Plays a role in AMPK levels and lipid oxidation in obesity.
ALA	Enhances mitochondrial biogenesis in skeletal muscle by promoting AMPK phosphorylation.

Source: Tanyıldız et al., (2021).

3. RELATIONSHIP BETWEEN EXERCISE AND AMPK

Regular physical activity is widely recognized as an effective strategy for reducing insulin resistance and lowering the risk of premature mortality and morbidity associated with cardiometabolic diseases. In contrast, physical inactivity and sedentary behavior are major risk factors for the development of obesity, type 2 diabetes, and cardiovascular diseases (Booth et al., 2011; Belli & Yaman, 2020).
During exercise, repeated muscle contractions increase cellular energy demand, leading to changes in intracellular adenine nucleotide ratios, particularly increases in AMP/ATP and ADP/ATP ratios. These changes generate metabolic stress and stimulate the activation of AMP-activated protein kinase (AMPK). Once activated, AMPK promotes glucose uptake and fatty acid oxidation while inhibiting anabolic processes, thereby contributing to the maintenance of cellular energy balance (Hardie et al., 2012).
In skeletal muscle, exercise-induced AMPK activation also contributes to insulin-independent glucose uptake by promoting the translocation of glucose transporter type 4 (GLUT4) to the cell membrane, which enhances glucose transport into muscle cells during and after exercise (Richter & Hargreaves, 2013).

Figure 1. Metabolic Regulation by AMPK



Source: Belli & Yaman (2020).

Regular exercise is widely recognized as an effective strategy for reducing insulin resistance and preventing early mortality and morbidity associated with cardiometabolic diseases. Conversely, physical inactivity and sedentary behavior represent major risk factors for the development of numerous chronic diseases. Because skeletal muscle accounts for approximately 70–80% of insulin-stimulated glucose disposal, maintaining skeletal muscle mass plays a critical role in preventing insulin resistance, type 2 diabetes, and other metabolic disorders (Pinto et a.l, 2023).

During exercise, repeated muscle contractions increase cellular energy demand, leading to alterations in intracellular adenine nucleotide ratios, particularly increases in AMP/ATP and ADP/ATP. These metabolic changes generate cellular energy stress and activate AMP-activated protein kinase (AMPK), which functions as a central regulator of cellular energy homeostasis (Belli & Yaman, 2020; Hardie et al., 2012).

Activated AMPK maintains metabolic balance by inhibiting ATP-consuming anabolic pathways, including fatty acid synthesis, cholesterol synthesis, and protein synthesis, while simultaneously stimulating ATP-producing pathways such as glucose uptake, glycolysis, and fatty acid oxidation (O'Neill, 2013).

One of the most potent physiological activators of AMPK is skeletal muscle contraction during exercise. Exercise-induced AMPK activation promotes the translocation of glucose transporter type 4 (GLUT4) to the plasma membrane independently of insulin, thereby increasing glucose uptake into skeletal muscle cells (Richter & Hargreaves, 2013). This process involves phosphorylation of Rab-GTPase-activating proteins such as TBC1D1 and TBC1D4 (AS160), which regulate GLUT4 vesicle trafficking.

AMPK also plays a key role in carbohydrate metabolism. It stimulates glycolysis by phosphorylating phosphofructokinase-2, thereby increasing the production of fructose-2,6-bisphosphate, an important activator of phosphofructokinase-1. In addition, AMPK inhibits glycogen synthesis through phosphorylation of glycogen synthase during periods of increased cellular energy demand (Halse et al., 2003).

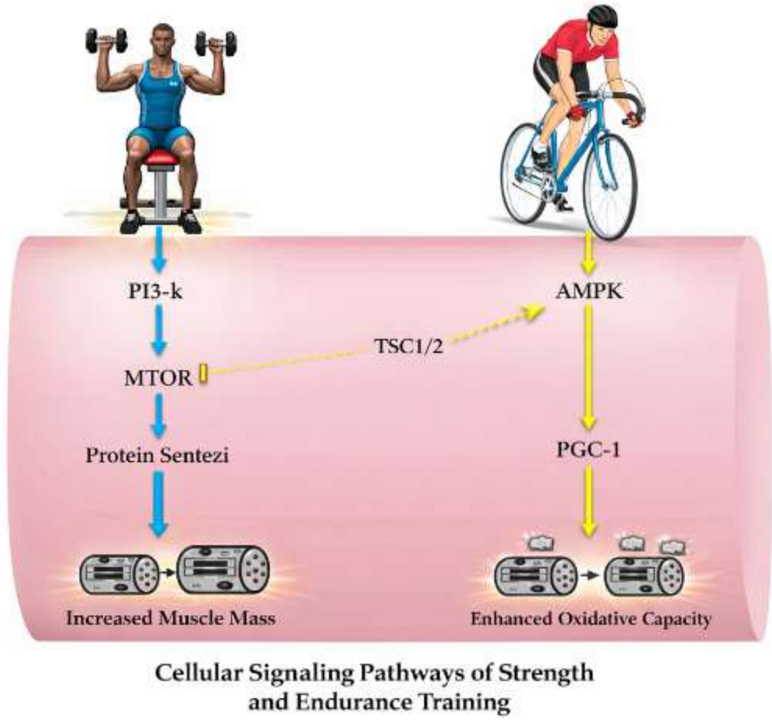
Beyond glucose metabolism, AMPK exerts significant regulatory effects on lipid metabolism. AMPK activation inhibits lipid synthesis by phosphorylating acetyl-CoA carboxylase (ACC), which reduces malonyl-CoA levels and relieves inhibition of carnitine palmitoyltransferase-1 (CPT-1), thereby promoting mitochondrial fatty acid β-oxidation (Bruce et al., 2006). AMPK also suppresses lipogenic gene expression by inhibiting sterol regulatory element-binding protein-1 (SREBP-1), thereby reducing fatty acid synthesis in liver and adipose tissue (Madsen et al., 2015).

In skeletal and cardiac muscle, AMPK facilitates fatty acid uptake through increased translocation of the fatty acid transporter CD36 to the plasma membrane, thereby enhancing substrate availability for β-oxidation. In cardiac tissue, AMPK also contributes to the regulation of both glucose and fatty acid metabolism and supports mitochondrial energy production through signaling pathways involving PGC-1α and FoxO transcription factors (Koonen et al., 2005).

In addition to regulating metabolic pathways, AMPK suppresses mammalian target of rapamycin (mTOR) signaling, a major regulator of protein synthesis. By inhibiting mTOR activity, AMPK prevents excessive protein synthesis and pathological cardiac hypertrophy (Gwinn et al., 2008).

Endurance exercise represents one of the most potent physiological stimuli for AMPK activation. Chronic endurance training promotes mitochondrial biogenesis and enhances GLUT4 expression, thereby improving metabolic flexibility and insulin sensitivity Experimental studies also demonstrate that endurance training increases phosphorylated AMPK (pAMPK) and SIRT1 signaling while reducing pro-apoptotic markers, suggesting that exercise may attenuate age-related alterations in skeletal muscle through AMPK-dependent pathways (Hardie et al., 2012).

Figure 2: Cellular Signaling Pathways of Strength and Endurance Training



Source: Hawley (2009).

4. CONCLUSION

Modern sedentary lifestyles and overnutrition have led to increased rates of obesity and diabetes. AMPK plays a central role in cellular energy homeostasis and appetite regulation by promoting catabolic and suppressing anabolic pathways upon activation.

Exercise robustly activates AMPK, enhancing insulin-independent glucose uptake via GLUT4, increasing fat oxidation, and regulating energy intake through hypothalamic pathways.

Strength and endurance training trigger different intracellular signals: endurance training emphasizes AMPK activation and mitochondrial adaptations, while strength training emphasizes mTORC1 activation and muscle growth. This interplay makes concurrent training a strategic area for further research.

Recommendations

Exercise Programming: Concurrent strength and endurance training may limit hypertrophy if not carefully programmed. Individualized periodization of training intensity and timing is key to optimizing both performance and health benefits.

Clinical Applications: Given AMPK's central role in energy metabolism, regular physical activity should be promoted in clinical protocols to prevent or treat obesity, diabetes, and metabolic syndrome.

Nutrition and Supplementation: Natural AMPK activators (e.g., resveratrol, curcumin, quercetin) show promise in enhancing performance and managing chronic diseases.

Future Research: More studies are needed to understand the long-term interactions between AMPK and mTOR under different training models, which could pave the way for targeted interventions in both athletic and clinical settings.

Conflict of Interest

There is no situation that may constitute a conflict of interest between the author(s) and any person, institution, or organization within the scope of this research.

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Contributions: Critical evaluation of the literature, scientific supervision, editorial and language revisions, and final approval of the manuscript

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