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AMPK and the Adaptation to Exercise

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Abstract

Noncommunicable diseases are chronic diseases that contribute to death worldwide, but these diseases can be prevented and mitigated with regular exercise. Exercise activates signaling molecules and the transcriptional network to promote physiological adaptations, such as fiber type transformation, angiogenesis, and mitochondrial biogenesis. AMP-activated protein kinase (AMPK) is a master regulator that senses the energy state, promotes metabolism for glucose and fatty acid utilization, and mediates beneficial cellular adaptations in many vital tissues and organs. This review focuses on the current, integrative understanding of the role of exercise-induced activation of AMPK in the regulation of system metabolism and promotion of health benefits.

Keywords

AMPK; exercise; metabolism; glucose uptake; fatty acid oxidation; adaptive responses

INTRODUCTION

Noncommunicable diseases (NCDs) caused 71% of all deaths (41 million) worldwide in 2018, reaching pandemic proportions (1). Regular exercise is indisputably the most powerful intervention for prevention and treatment of most NCDs. However, despite decades of research, the underlying mechanisms by which exercise training induces the health benefits are poorly understood. This is particularly true for the molecular and signaling mechanisms that modulate the adaptive processes of exercise. One such signaling modulator of exercise adaptation is AMP-activated protein kinase (AMPK), which is ubiquitously expressed in literally all cells, tissues, and organs, including the skeletal muscle, heart, liver, adipose tissue, and brain. Ever since its discovery in the 1970s during the search for a kinase that regulates 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase in control of cholesterol synthesis (2), attention has been drawn to many other regulatory functions of this kinase, including its regulatory roles in the metabolic and cellular processes induced

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by exercise in the aforementioned tissues and organs (3, 4). AMPK is a highly conserved serine/threonine kinase that plays a critical role in energy homeostasis. AMPK monitors energy availability and positively regulates glucose and fatty acid uptake and oxidation and catabolic pathways, such as autophagy. Simultaneously, AMPK negatively regulates fatty acid, sterol, and protein synthesis and other anabolic processes (5, 6). Previous reviews have eloquently discussed the role of AMPK in cellular metabolism and adaptation (6–8). This review focuses on an integrative understanding of exercise-induced AMPK activation in cellular and metabolic adaptations in vital tissues and organs, including skeletal muscle, heart, liver, adipose tissue, and brain. We also review the evidence of exercise-induced AMPK activation in mitigating NCDs.

AMPK STRUCTURE AND FUNCTION

AMPK is a heterotrimer composed of alpha (α1 or α2 isoform), beta (β1 or β2 isoform), and gamma (γ1, γ2, or γ3 isoform) subunits. The α subunit contains the catalytic domain, whereas the β subunit functions as scaffolding to link the α and γ subunits. The γ subunit senses relative levels of AMP or ADP to ATP to induce conformational change of the α subunit in favor of AMPK activation through phosphorylation by upstream kinases. The γ subunit possesses four cystathionine-β-synthase (CBS) domains, of which only CBS1, CBS3, and CBS4 bind AMP/ADP/ATP (9, 10). The binding of AMP or ADP to the γ subunit contributes to three mechanisms of AMPK activation: (*a*) allosteric activation, (*b*) promotion of AMPK activation by phosphorylation of the α subunit at threonine 172 (Thr172), and (*c*) inhibition of protein phosphatases, preventing dephosphory-lation at Thr172 (9, 11). Of particular interest is the mechanism by which AMPK is activated by upstream kinases, as these can be activated by different cellular cues, making AMPK activation more versatile. It is now known that AMPK activation by phosphorylation of Thr172 is achieved by liver kinase B1 (LKB1) and calcium/calmodulin-dependent protein kinase 2 (CaMKK2). Activated AMPK exerts its roles over metabolic regulation and cellular adaptive processes by phosphorylating downstream effectors, leading to their activation or inhibition. AMPK activation has been implicated in the regulation of glucose, lipid, and protein metabolism as well as cellular adaptive processes, such as autophagy and mitochondrial remodeling.

AMPK ACTIVATION BY EXERCISE IN SKELETAL MUSCLE METABOLISM AND ADAPTATION

In response to exercise, there is a dramatic increase in energy demand in skeletal muscle that requires increased energy turnover. Exercise-induced molecular signaling is intimately involved in the regulation of metabolism to meet the need of increased energy demand and adaptive cellular processes to prepare for future challenges. Muscle contractions during exercise lead to increases in calcium, nitric oxide, reactive oxygen species, and AMP/ADP as cues of stress, which in turn activate many kinases and signaling pathways, such as mitogen-activated protein kinases (ERK, p38, JNK), CaMKKs, and AMPK (7). Activation of these signaling pathways contributes to not only increased glucose and fatty acid uptake and oxidation as a fuel source to maintain exercise but also adaptative processes

critical for enhanced muscle contractile and metabolic functions in the long run. AMPK has been strongly implicated in these regulatory processes, as activation of AMPK with increased Thr172 phosphorylation and activity occurs during and immediately after exercise (Figure 1). The first direct evidence of AMPK activation in skeletal muscle by exercise was reported in rats following as little as 5 min of treadmill running with concurrent reduction of acetyl-CoA carboxylase (Acc) activity, possibly through phosphorylation at serine 79 (Ser79) of Acc1 and Ser212 of Acc2, and malonyl-CoA concentration (12). Cycling exercise of moderate intensity (90 min) in humans resulted in increased AMPK activity and phosphorylation in muscle biopsies (13). Treadmill running in mice resulted in increased phosphorylation of AMPK at Thr172 in all recruited glycolytic and oxidative muscles (14). Because ADP increases from approximately 40 μM to between 130 and 200 μM, which is above the K_d of AMPK (80 μM) during moderate to high-intensity exercise, while AMP increased significantly but stayed below the K_d of AMPK, Oakhill et al. (15) argued that ADP is the predominant agonist of AMPK in skeletal muscle during exercise. Furthermore, pharmacological activation of AMPK in skeletal muscle by 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (AICAR), an endogenous substrate that can induce accumulation of 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranosyl monophosphate (ZMP) to mimic AMP, indicates that AMPK activation is sufficient to promote glucose and fatty acid uptake and oxidation (16–20). An elegant global phosphoproteomics analysis of human skeletal muscle biopsies after acute exercise in untrained healthy individuals revealed more than 1,000 phosphosites, of which 55 overlapped with the phosphosites found in AICAR-stimulated myotubes in cell culture (21). This is to date the most comprehensive analysis of the AMPK phos-phoproteome network in skeletal muscle in the context of exercise. These findings suggest that exercise-induced AMPK activation may cause the increased glucose and fatty acid uptake and oxidation in skeletal muscle. However, it was not until the recent advancements in molecular genetics that animal models of AMPK gene deletions allowed studies to address whether AMPK activation is required for exercise-induced glucose and fatty acid uptake and oxidation in skeletal muscle.

Glucose Uptake and Insulin Sensitivity

During exercise, an immediate increase in glucose uptake by the muscle cells is needed as fuel to maintain exercise. Muscle contractions stimulate glucose transporter type 4 (GLUT4) translocation from storage vesicles to the surface of the sarcolemma, the plasma membrane of muscle, which permits facilitated diffusion of glucose down its concentration gradient into the muscle cells (Figure 1). Two important proteins that regulate GLUT4 mobilization are TBC1 domain family member 1 (TBC1D1) and TBC1D4 (AS160). TBC1D1 and TBC1D4 promote GLUT4 translocation to the sarcolemma by inhibiting Rab-GTPase-activating protein (Rab-GAP). Phosphorylation of TBC1D1 and TBC1D4 can occur at many sites on each protein, some of which are phosphorylated by AMPK. AMPK has long been considered a critical kinase in promoting exercise-induced glucose uptake. This notion has been supported by evidence of the pharmacological activation of AMPK by AICAR, which has been shown to be sufficient to induce translocation of GLUT4 to the sarcolemma (22–24), resulting in increased glucose uptake (25). However, the evidence for a definitive role of AMPK activation in exercise-induced glucose uptake is somewhat conflicting and has

led to a dispute over the causal role of AMPK activation in the increased glucose uptake during exercise (26). An early study reported that muscle-specific AMPKβ1β2 knockout (AMPKβ1β2 MKO) mice have reduced clearance of glucose during exercise, suggesting that AMPK activation is required for increased glucose uptake by working skeletal muscle (27). Conversely, more recent studies in muscle-specific AMPKα1α2 KO (AMPKα1α2 MKO) and in tamoxifen-inducible, muscle-specific AMPKα1α2 KO mice (AMPKα1α2 iMKO) suggested that AMPK is not required for exercise-induced glucose uptake (28, 29). In addition to exercise, muscle contraction by electric stimulation has also been used to induce glucose uptake and assess the role of AMPK activation. Some researchers found that AMPK activation is not required in contraction-induced glucose uptake in a variety of AMPK gene depletion models (16, 30–32), but others found contraction-induced glucose uptake is impaired in muscle-specific AMPKα2 kinase-dead (AMPKα2 KD) transgenic mice, suggesting that contraction-induced glucose uptake is dependent on AMPK activation (17, 33). Tbc1d1 and Tbc1d4 can be phosphorylated by AMPK, but these events are not required for glucose uptake (34). Phosphorylation of Tbc1d1 at Ser231 and Tbc1d4 at Ser711 is elevated during in situ contraction, which is abated in AMPKα1α2 MKO mice, suggesting that these phosphorylation sites are caused by AMPK activation (Figure 1). However, glucose uptake is normal in these KO animals during contraction, suggesting that these phosphorylation events are not important in glucose uptake during exercise (34). As pointed out by previous publications (26, 29), glucose uptake was measured after muscle contraction. The remaining possibility is that AMPK-mediated phosphorylation of these substrates regulates glucose uptake during recovery from exercise.

In support of a role for AMPK activation in promoting glucose uptake during recovery from exercise, a recent study of AMPKα1α2 MKO and AMPKα1α2 iMKO mice confirmed that AMPK is not required for glucose uptake during exercise but is required for this process during recovery (29). The authors proposed that AMPK activation delays Glut4 endocytosis (through internalization of Glut4 back to storage vesicles in the cytosol) while insulin and muscle contraction increase Glut4 exocytosis. Both mechanisms ultimately act to elevate Glut4 abundance on the sarcolemma. Studies in global Tbc1d1 KO mice confirmed the role of Tbc111 in glucose uptake during recovery from exercise (29). Together, these data suggest that the AMPK-TBC1D1 axis regulates muscle glucose during recovery from exercise. It is of note that all of the genetic interventions were either global or muscle-specific deletions of the AMPK genes or the muscle-specific overexpression of a dominant negative kinase-dead AMPK isoform, which inevitably disrupt stoichiometry and/or elicit compensatory changes that may confound some of the analyses. Thus, there is an urgent need to develop more sophisticated molecular genetic animal models with targeted mutations of AMPK activation phosphorylation sites, such as Thr172, and of the AMPK phosphorylation sites of the effector proteins to definitively prove the role of AMPK activation to control glucose uptake during and after exercise.

A single bout of endurance exercise or repeated muscle contractions promote muscle insulin sensitivity several hours later. Because AMPK is activated by exercise or muscle contraction, the question is whether AMPK activation is causal to the enhanced insulin sensitivity in skeletal muscle. Kjøbsted et al. (34) showed that in situ contraction and in vivo treadmill running increase muscle and whole-body insulin sensitivity in wild-type

(WT) mice, respectively, but not in AMPKα1α2 MKO mice. The data strongly support that AMPK activation is necessary for improved insulin-stimulated glucose uptake following an acute bout of exercise. This is likely mediated by the AMPK-TBC1D4 signaling axis, as enhanced insulin-stimulated Tbc1d4 Thr649 (equivalent to Thr642 in human TBC1D4) and Ser711 phosphorylation by prior in situ contraction is abolished in AMPKα1α2 MKO mice (34). Similarly, prior activation of AMPK with AICAR increases insulin sensitivity and insulin-induced glucose uptake, which are absent in AMPKα1α2 MKO mice. Importantly, prior treatment with AICAR causes greater Tbc1d4 phosphorylation at Thr649 and Ser711 under the condition of insulin stimulation (35). These findings support the role of AMPK activation during exercise or muscle contraction in promoting insulin sensitivity in skeletal muscle converging on signaling molecules that control GLUT4 trafficking as a mechanism of the benefit of exercise (Figure 1). Targeting this pathway may prove to be an effective intervention against insulin resistance and type 2 diabetes.

Fatty Acid Uptake and Oxidation

Fatty acid uptake by muscle cells requires fatty acid translocase (CD36), fatty acid–binding protein (FABP), and fatty acid transport protein (FATP) (36). Once inside the cell, fatty acids are converted to fatty acyl-CoA by acyl-CoA synthetase for oxidation or further storage. Acyl-CoA can be shuttled into the mitochondria through carnitine palmitoyl transferase 1 (CPT1) for β oxidation. Acyl-CoA transport into the mitochondria is, under basal condition, limited due to the inhibitory function of the ACC product, malonyl-CoA, toward CPT1. Malonyl-CoA concentrations are reduced, and fatty acid oxidation is increased during exercise (37). When AMPK is activated, ACC is directly phosphorylated by AMPK, resulting in reduced ACC activity, and this AMPK activation-mediated ACC inhibition is therefore considered responsible for enhanced fatty acid oxidation during exercise (12, 22, 38) (Figure 1).

In support of evidence of a causal role of AMPK activation in increased fatty acid oxidation in skeletal muscle during exercise, AMPKα1α2 MKO mice show a greater respiratory exchange ratio, a physiological parameter of carbohydrate oxidation over fatty acid oxidation measured by calorimetry, during treadmill exercise compared with WT mice (39). Findings from muscle contractions of isolated muscles in the same study further support this. However, these animals also have reduced levels of Cd36 and Fabp (39); these unwanted changes in proteins important for fatty acid transportation could result in decreased fatty acid uptake capacity, confounding interpretation of the role of AMPK activation in controlling fatty acid oxidation during exercise. Indeed, there are conflicting findings suggesting that AMPK is not required for fatty acid uptake and oxidation during exercise. In several AMPK loss-of-function genetic models, the respiratory exchange ratio during exercise is decreased or unchanged, suggesting that fatty acid utilization is increased or unchanged in the absence of AMPK activation (27, 40). Additionally, fatty acid utilization during muscle contraction is not impaired in AMPK loss-of-function genetic models (20, 27, 28, 31, 40). Therefore, further studies are needed to ascertain the definitive role of AMPK activation in controlling fatty acid oxidation during exercise, as the current genetic models are inherently disruptive of the stoichiometry of the metabolic network in skeletal muscle that regulates fatty acid metabolism.

Altogether, the data described above suggest that AMPK may be dispensable for increased fatty acid oxidation during exercise, but there are data to support a role of AMPK in fatty acid oxidation during recovery from exercise. AMPKα2 KO mice have lower fatty acid oxidation concurrent with higher glucose oxidation compared with WT mice during recovery from a bout of treadmill running, suggesting that AMPK, at least the dominant α2 isoform in skeletal muscle, is required for enhanced fatty acid oxidation during recovery from exercise (41). The same study showed that AMPK activation is necessary for induced protein expression of pyruvate dehydrogenase kinase 4 (Pdk4) during recovery. Because PDK4 can directly phosphorylate pyruvate dehydrogenase at its inhibitory phosphorylation site Ser293, and pyruvate dehydrogenase is responsible for the conversion of pyruvate to acetyl-CoA for oxidation, AMPK-dependent PDK4 activation may be responsible for the inhibition of glucose oxidation and promotion of fatty acid oxidation during recovery from an acute bout of exercise (41). Collectively, these data point to AMPK as a regulator of energy homeostasis and substrate partitioning.

Exercise Adaptations

Exercise-induced skeletal muscle adaptations ensure an improved ability to deal with future metabolic or contractile challenges. It is well known that endurance exercise training leads to numerous phenotypic changes, including improved mitochondrial quality, increased glucose uptake, and enhanced insulin sensitivity. Because we know that AMPK activation occurs in response to muscle contraction and exercise, a fundamentally important question is whether AMPK activation in skeletal muscle underlies the adaptive responses and processes induced by exercise. In an early study, Rodnick et al. (42) showed that voluntary wheel running induces an increase in Glut4 expression in rat plantaris muscle, a muscle that is heavily recruited during this habitual exercise. Later, many animal studies showed that endurance exercise training promotes *Glut4* mRNA and protein expression in recruited skeletal muscles, which is considered one of the major metabolic adaptations to endurance exercise (7). However, studies using molecular genetic models suggest that AMPK is dispensable for the increase in Glut4 abundance following exercise training. For example, four weeks of treadmill training or wheel running in global AMPKα2 KO mice led to similar degrees of increased Glut4 protein and transcript compared to WT mice, suggesting that AMPK is not required for these adaptations (43, 44). A recent study of two-week endurance training in rat triceps transfected with dominant negative AMPK showed reduced basal Glut4 but a similar percentage increase of Glut4 after exercise training. This suggests that AMPK plays a role in controlling basal GLUT4 expression in skeletal muscle but is not required for the exercise training-induced GLUT4 upregulation (45).

Enhanced mitochondrial function in skeletal muscles is one of the most important cellular adaptations induced by endurance exercise, where mitochondria remodeling occurs to achieve optimal function through a collection of processes of mitochondrial biogenesis, mitochondrial dynamics, and mitophagy. AMPK has been implicated in promoting mitochondrial remodeling in skeletal muscle in response to exercise training. Regarding the regulation of mitochondrial biogenesis, it has been shown that both endurance exercise and pharmacological activation of AMPK in skeletal muscle stimulate gene expression of peroxisome proliferator-activated receptor gamma coactivator 1 alpha (*PGC-1α*), a

master regulator of mitochondrial biogenesis (46). Using primary muscle cells and *Pgc-1α* KO mice, Jäger et al. (47) showed that AMPK phosphorylates Pgc-1α protein directly at Thr177 and Ser538 both in vivo and in vitro, and these phosphorylation events are required for the Pgc-1α-dependent induction of the *Pgc-1α* promoter (Figure 1). Importantly, both AMPKβ1β2 and AMPKα1α2 MKO mice have reduced mitochondrial biogenesis, mitochondrial content, and impaired mitochondrial function (27, 30). Increases of mitochondrial content in response to 6.5 weeks of exercise training are blunted in dominant negative AMPKα2 KD transgenic mice, suggesting that exercise training–induced mitochondrial biogenesis is AMPK dependent (48). In contrast, AMPKα2 KO mice have been shown to have normal increases of mitochondrial protein abundance after two weeks of exercise training, suggesting that AMPK is not essential for mitochondrial adaptation in skeletal muscle in response to exercise (44). In summary, the role of AMPK in promoting skeletal muscle mitochondrial biogenesis in response to exercise training is not yet fully elucidated.

AMPK activation has also been implicated in controlling mitochondrial dynamics in response to exercise. In a rat model of endurance exercise, Ding et al. (49) showed reduced mitofusin 1/2 (*Mfn1/2*) mRNA and protein as well as increased mitochondrial fission 1 (*Fis1*) mRNA and protein during a relatively long duration of treadmill running (150 min). This suggests changes in mitochondrial dynamics that favor mitochondrial fission. In a recent study, Laker et al. (50) showed that exercise-induced Drp1 phosphorylation at Ser616 and Ser637 remains intact in muscle-specific dominant negative AMPKα1 KD transgenic mice, whereas muscle-specific AMPKγ1 constitutively active transgenic mice have normal Drp1 phosphorylation at both sites. These findings suggest that Drp1 is phosphorylated by another kinase during exercise. Recent proteomic and bioinformatic screens have identified two phosphorylation sites, Ser155 and Ser173, of the mitochondrial fission factor (MFF) (51), the primary receptor for DRP1 on the mitochondrial outer membrane for mitochondrial fission (Figure 1). Indeed, activation of AMPK causes the localization of DRP1 to mitochondria that are dependent on AMPK-mediated MFF phosphorylation (51). Thus, AMPK activation may promote mitochondrial fission by phosphorylating MFF, which in turn controls the localization of DRP1. Finally, an AMPK activation compound, 991, stimulates mitochondrial fission via phosphorylation of Mff at Ser146 (equivalent to human Ser172) and induces mitophagy in cultured muscle cells (52). It is unknown whether exercise-induced AMPK activation is required for MFF phosphorylation and the consequential changes in mitochondrial dynamics.

Finally, exercise may also activate mitophagy through AMPK activation in skeletal muscle. Laker et al. (50) recently showed that a single bout of treadmill running is sufficient to induce mitophagy in skeletal muscle. Because mitophagy activation in response to acute exercise requires the simultaneous activation of several processes (e.g., autophagosome biogenesis, mitochondrial fission, and autophagosome-lysosome fusion), it makes biological sense to have an energy sensor kinase as a critical node for coordinated activation of these converging processes. Using muscle-specific dominant negative AMPKα1 KD and constitutively active AMPKγ1 transgenic mice, Laker et al. (50) confirmed that immediately following an acute bout of endurance exercise in mice, AMPK is necessary and sufficient for increased phosphorylation of Unc-51-like autophagy activating kinase 1 (Ulk1) at Ser555

in skeletal muscle; Ulk1 is a kinase required for mitophagy (53) (Figure 1). Importantly, both muscle-specific dominant negative AMPKα1 KD transgenic mice and Ulk1 MKO mice showed impaired mitophagy following a single bout of treadmill running, suggesting that activation of the AMPK-ULK1 regulatory axis is required for exercise-induced mitophagy.

Taken together, activation of AMPK and the resulting activation of downstream effectors may together stimulate mitochondrial biogenesis, mitochondrial fission, and mitophagy to promote mitochondrial quality and function in skeletal muscle, which are fundamentally important for skeletal muscle metabolic and contractile functions. While this review was written, Drake et al. (54) reported that specific isoforms of AMPKα1/α2/β2/γ1 are localized on the outer mitochondrial membrane, referred to as mitoAMPK, in various tissues in mice and humans. mitoAMPK is activated by mitochondrial energetic stress, and inhibition of mitoAMPK activity attenuates exercise-induced mitophagy in skeletal muscle in vivo. These findings support that mitoAMPK-mediated mitochondrial quality control underscores the complexity of sensing cellular energetics and controlling mitochondrial adaptation in vivo.

AMPK ACTIVATION BY EXERCISE IN CARDIAC METABOLISM AND FUNCTION

During exercise, the body needs to increase cardiac output three- to fourfold to meet the demand for oxygen in working muscles. Animal studies indicate that acute exercise and exercise training increase cardiac AMPK phosphorylation and activity (55, 56) (Figure 2). Exercise and in vitro cardiomyocyte contraction increase fatty acid uptake and glucose uptake along with Glut4 translocation to the sarcolemma of cardiac myocytes (56, 57). AMPK activation by AICAR in rat ventricular papillary muscles increases Glut4 translocation and glucose uptake (58). Furthermore, pharmacological activation of AMPK results in increased fatty acid uptake and oxidation in isolated cardiomyocytes concurrent with increased mRNA and protein expression of fatty acid uptake proteins, Fat/Cd36 and Got2 (equivalent to human FABPpm), which are abolished by the AMPK inhibitor adenine 9-β-D-arabinofuranoside (59). Lastly, AICAR treatment increases sar-colemmal levels of Fat/Cd36 and Glut4, suggesting that AMPK activation increases both fatty acid and glucose uptake in cardiomyocytes (57). Collectively, these studies suggest that AMPK activation is sufficient to induce glucose and fatty acid metabolism (Figure 2), but a causal relationship between AMPK activation in control of cardiac metabolism has not been ascertained or elucidated.

It is well known that exercise training promotes metabolic and structural adaptations in the heart. Depending on the type, intensity, and duration of exercise, the adaptations lead to improved energetic and contractile machineries that better sustain cardiac contractility. In fact, regular exercise has emerged as a powerful intervention for many cardiovascular disease conditions, such as chronic heart failure. Using a mouse model of pathological cardiac hypertrophy with fibrosis, Ma et al. (55) showed that four weeks of swim training alleviate isoproterenol-induced cardiac fibrosis and oxidative stress in WT but not AMPKα2 KO mice. In another model of heart failure, exercise training (four weeks of treadmill

running) in rats attenuates transverse aortic constriction–induced cardiac dysfunction, fibrosis, and endoplasmic reticulum stress-related apoptosis. It also significantly improves autophagy and increases AMPK phosphorylation, both of which are abolished by AMPK inhibitor compound C or autophagy inhibitor 3-methyladenine (60). These findings suggest that exercise training can alleviate pressure overload–induced left ventricle dysfunction and remodeling via AMPK-dependent autophagy (Figure 2). Importantly, voluntary wheel running in WT mice results in a 53% increase of protein expression of sarco/endoplasmic reticulum Ca^{2+}-ATPase (Serca2a) in the heart, a cornerstone molecule for restoring cytosolic concentration of Ca^{2+} during the diastole of the cardiac cycle (61). In contrast, dominant negative AMPKα2 KD transgenic mice display a reduction in basal Serca2a expression and an absence of induction by exercise (61). These findings strongly support the importance of AMPK activation by exercise in the heart in mediating adaptive responses against cardiac dysfunction under various disease conditions. It is worth noting that treatment with a pan-AMPK activator, MK-8722, improves whole-body glucose homeostasis but promotes cardiac hypertrophy and glycogen accumulation in rodents and rhesus monkeys (23). Another pan-AMPK activator, O304, increases cardiac glucose uptake, reduces cardiac glycogen levels, and improves cardiac function in mice with no complication of cardiac hypertrophy (62). Thus, pharmacological activators of AMPK may have therapeutic potential for cardiometabolic disorders.

AMPK ACTIVATION BY EXERCISE IN HEPATIC GLUCONEOGENESIS AND LIPID METABOLISM

The liver is critical in maintaining whole-body glucose homeostasis within a narrow range under energy-demanding conditions such as exercise (63). Exercise typically causes an increase in glucose production through glycogenolysis and gluconeogenesis (64). These processes result in glucose release from the liver during short-term, moderate exercise concurrent with an elevated glucose disposal primarily in the working muscle and heart to maintain the circulating glucose level. Hepatic glucose production is controlled by many hormones released during exercise (65). Specifically, glucagon released from pancreatic α cells promotes glycogenolysis and gluconeogenesis in the liver (66). Importantly, enhanced glucose synthesis requires extensive consumption of ATP (67), which results in energetic stress and an elevated AMP/ATP ratio, a strong cue for AMPK activation. It has been hypothesized that glucose homeostasis is regulated by AMPK because endurance exercise, both acute and long term, increases phosphorylation of AMPK in the liver (12, 68–72) (Figure 3). However, evidence from molecular genetic models is somewhat counterintuitive to physiological conditions. For example, liver-specific Lkb1 or AMPKα2 KO mice exhibit hyperglycemia (73, 74), whereas liver-specific overexpression of AMPKα2 has the opposite change in blood glucose (75). Importantly, these findings were obtained at rest and therefore may not reflect the metabolic responses influenced by AMPK activation under the condition of exercise. More relevant evidence of the role of AMPK activation in controlling hepatic glucose homeostasis comes from a study in which liver-specific AMPKα1α2 KO (AMPKα1α2 LKO) mice fail to maintain euglycemia during exercise due to reduced glycogenolysis, whereas gluconeogenesis remains at a normal level (64). However, AMPKα1α2 LKO mice have reduced glycogen deposition in the liver, which

can impede glycogenolysis. Nevertheless, these findings show that AMPK activation is not required for exercise-induced gluconeogenesis in the liver.

Exercise appears to also promote insulin sensitivity in the liver. A single bout of treadmill running (60 min) in mice results in increased insulin sensitivity in the liver and stimulates transcription of genes important for hepatic gluconeogenesis, such as *Pdk4*, *Pgc-1α*, glucose 6-phosphatase (*G6pc*), and phosphoenolpyruvate carboxykinase (*Pck1*), concurrent with activation of AMPK (Thr172 phosphorylation) (71). Similar findings were observed in gene transcript levels with delayed increases of Pck1, G6pc, and Pdk4 proteins in mouse liver following a similar treadmill running regime (76). Pgc-1α functions as a transcriptional coactivator to increase *Pdk4* gene expression along with increased transcription of the other gluconeogenic genes, *G6pc* and *Pck1* (77, 78). *Pdk4* inhibits glucose oxidation and promotes gluconeogenesis by phosphorylating and inactivating the pyruvate dehydrogenase complex (79). To date, there is no experimental evidence of the causal role of AMPK activation by exercise in the liver in controlling hepatic gluconeogenic gene expression.

Recently, liver AMPK activation has emerged as a potential target for treatment of nonalcoholic fatty liver disease (NAFLD), which is becoming one of the most common diseases worldwide. NAFLD in 25% of patients progresses into nonalcoholic steatohepatitis (NASH). A hall-mark of this disease is increased triglycerides content in the liver (80). Activation of liver AMPK leads to the inhibition of ACC and, consequently, increased fatty acid oxidation, which may underlie the mechanism by which AMPK activation reduces NAFLD (81). Broadly, both aerobic and resistance exercise training are effective in treating NAFLD and reducing liver fat mass and liver triglycerides in mouse models (82–84). Exercise training also decreases the progression of fibrosis, enhances regenerative capacity, and reduces the occurrence of hepatocellular carcinoma, which develops in late stage NAFLD (84–86). AMPK activator AICAR is sufficient to recapitulate these beneficial effects of exercise training (86). Similarly, increased phosphorylation of AMPK is associated with improvements in NAFLD (80). These findings suggest that AMPK activation counteracts NAFLD by increasing fatty acid oxidation (81). However, studies of genetically engi-neered knock-in (KI) mice with mutations of AMPK phosphorylation sites in both Acc1 and Acc2 indicated that six weeks of high-intensity interval training have similar impacts on levels of ala-nine aminotransferase and aspartate transaminase, the markers of liver injury, in obese KI and WT mice. Training also suppresses hepatic glucose production induced by insulin to the same degree in these mice. Finally, endurance exercise training (eight weeks) in high-fat diet–induced obese mice results in reduced lipid droplet formation, decreased hepatic triglyceride, and enhanced lipophagy by activating the AMPK-Ulk1 regulatory axis (87). Additional research is clearly needed to better understand the functional role of AMPK activation and downstream events in response to exercise training in treating NAFLD/NASH.

AMPK ACTIVATION BY EXERCISE IN LIPOLYSIS AND BROWNING OF WHITE ADIPOSE TISSUE

Adipose tissue functions to liberate fatty acids from triacylglycerides, referred to as lipolysis, and release them into the circulation to be oxidized for energy production by other issues, including the skeletal muscle and the heart. Increased energy demand from exercise leads to increased lipolysis and reesterification in adipose tissue (88). Exercise induces AMPK activation in the adipose tissue during and after exercise, as well as after exercise training (68, 89, 90). AMPK activation in adipose tissue in response to endurance exercise appears to be dependent on β-adrenergic receptor activation induced by adrenaline (90) and is mediated by the process of lipolysis (91). As lipolysis and free fatty acid reesterification increase, the energy charge is depleted, resulting in increased AMPK activity (92) (Figure 4). AMPK activation may play a feed-forward role in lipolysis because adrenaline-induced lipolysis in isolated adipocytes can be blocked by compound C, an AMPK inhibitor (90). Interestingly, adipose tissue–specific AMPKα1α2 KO mice (AMPKα1α2 AKO) display normal fasting blood glucose, glucose tolerance, and insulin tolerance compared with WT mice (93). A definitive role of adipose tissue AMPK activation in controlling lipolysis remains to be elucidated.

Exercise training, particularly endurance exercise, is a potent lifestyle intervention against obesity. A single bout of swimming (120 min) in mice leads to reduced peroxisome proliferator-activated receptor γ2 (*Pparg2*) and CCAAT enhancer binding protein α (*Cebpa*) mRNA expression, with a concurrent increased expression of *Cebpb*, *Cebpd*, *Pgc-1α*, and *Ucp1* in white adipose tissue (WAT) (94), suggesting that acute exercise suppresses adipogenic genes and promotes thermogenic genes. Exercise training also increases Pgc-1α expression and mitochondrial enzymes in adipose tissue, supportive of mitochondrial adaptation to exercise (95–97). AMPK activation by AICAR increases *Pgc-1α* mRNA expression in WAT (98). AMPKβ1 KO mice also have attenuated adipose tissue *Pgc-1α* mRNA expression under the condition of norepinephrine stimulation, suggesting that AMPK regulates PGC-1α and increases expression of mitochondrial proteins in adipose tissue (99) (Figure 4). Importantly, adipose-specific, inducible AMPKβ1β2 KO (AMPKβ1β2 iAKO) mice are cold intolerant and resistant to β-adrenergic activation of brown adipose tissue (BAT) and beiging of WAT, a conversion of WAT to BAT. These mice have impaired mitochondria structure and function and reduced markers of mitophagy in BAT with impaired thermogenic programs induced by chronic β-adrenergic activation (100). Overall, the role of adipose tissue AMPK activation in conversion of WAT to BAT remains unknown.

AMPK ACTIVATION BY EXERCISE IN BRAIN ADAPTATION AND COGNITIVE FUNCTION

Increasing evidence shows that regular exercise promotes mental health and cognitive function. In particular, exercise training has been shown to promote adult hippocampal neurogenesis and neuronal plasticity along with increased memory and cognitive function (101, 102). Evidence from three animal exercise models shows enhanced AMPK activity by exercise training in the hippocampus of the brain. In an accelerated aging model of

d-galactose-treated rats, reduced protein expression of the AMPK/Sirt1/Pgc-1α signaling pathway is restored after 12 weeks of swimming (103). Similarly, treadmill running (10 weeks) in old rats results in increased expression and phosphorylation of Camk2a and AMPKα1 (104). Finally, voluntary wheel running restores AMPK activity and its phosphorylation in the hippocampus of senescence-accelerated mice P8 (SAMP8), with enhanced expression of mitochondrial proteins (105) (Figure 5). However, no studies show direct evidence of exercise-induced AMPK activation in the hippocampus in response to an acute bout of exercise. The aforementioned restoration of AMPK expression and phosphorylation could be a consequence of the neuronal impact of exercise training.

Evidence of the benefits of exercise training for the brain continues to increase. Treadmill running (10 weeks) in old rats restores intersessional habituation and hippocampus morphology with reduced oxidative stress and enhanced autophagy markers (104) (Figure 5). A similar but slightly shorter-term exercise regimen (3 weeks) rescues the learning and memory deficits in restraint-stressed mice. It also restores the expression of brain-derived neurotrophic factor (Bdnf), a key molecule in plastic changes related to learning and memory; synaptophysin, a glycoprotein that is an integral part of the neuroendocrine secretory granule membrane; and postsynaptic density protein 95, a pivotal postsynaptic scaffolding protein in excitatory neurons. These changes are mimicked by 7 days of AICAR treatment (106). Treadmill running (4 weeks) rescues spatial learning and memory in mice with amyloid β injection into the cornu ammonis 1 (CA1) area of the hippocampus and restores the phosphorylation of AMPK and expression of Pgc-1α, fibronectin type III domain containing 5 (Fndc5), and Bdnf (107) (Figure 5). Finally, voluntary wheel running attenuates corticosterone-induced depression-like behavior in mice and improves neurogenesis and dendritic plasticity in the hippocampus (108). Together, these findings illustrate the many benefits of exercise training in deterring pathological changes and rescuing functional deficits in various neurodegenerative disease conditions. However, the role of AMPK activation in mediating these exercise benefits remains unexplained.

CONCLUSIONS

Exercise-induced adaptations in various tissues and organs promote health and prevent disease, and AMPK activation may play a critical role in conferring these benefits. Exercise and treatment with AMPK activators promote similar metabolic and cellular adaptations leading to improved energy homeostasis. The existing findings show that AMPK is an attractive target for prevention and treatment of NCDs. Advances in sophisticated molecular genetic models in animals will allow future experiments to improve our mechanistic understanding of the causal effects of AMPK activation in various tissues and organs during acute exercise and recovery as well as in response to exercise training.

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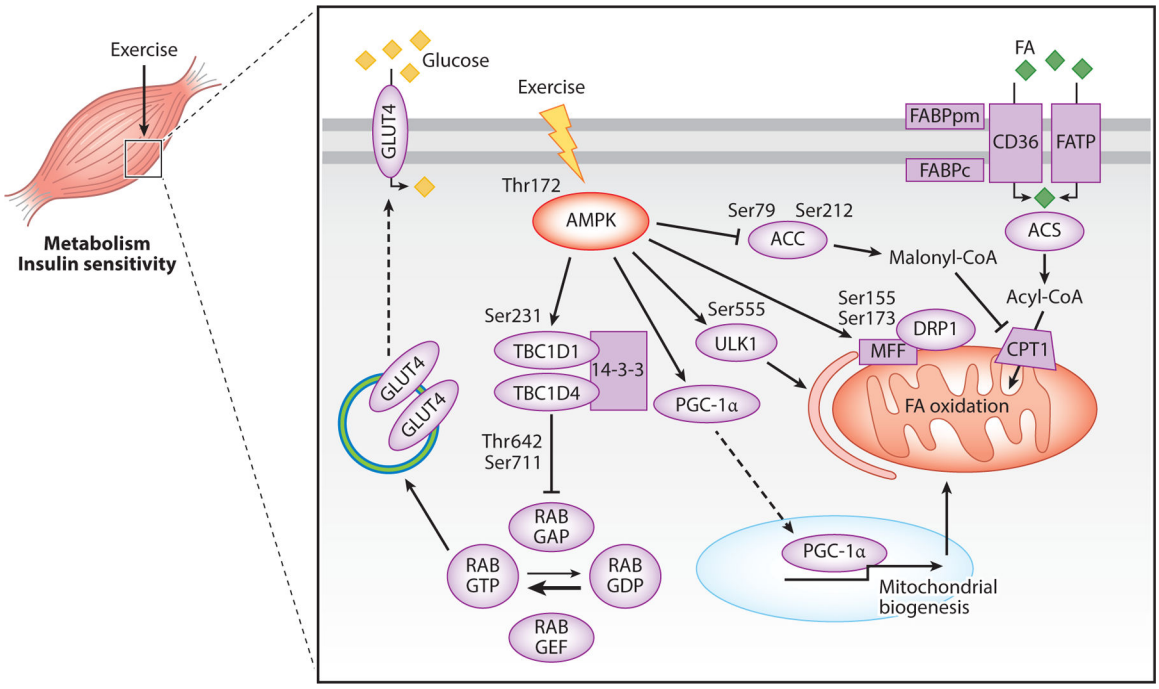

Figure 1.

Mechanisms by which exercise-induced AMPK modifies metabolism in skeletal muscle. Phosphorylation of AMPK at Thr172 increases glucose uptake by phosphorylating TBC1D1 and TBC1D4, thus promoting their binding to 14-3-3, which inhibits RAB GAP activity. This leads to increased RAB GTP, which promotes mobilization of GLUT4 to the membrane. AMPK activation also increases FA oxidation. FAs are taken up into the cell by a group of FA transport proteins; FAs are then converted to acyl-CoA and taken into the mitochondria by CPT1 for oxidation. AMPK activation promotes FA uptake by phosphorylating and inhibiting ACC. This inhibits ACC synthesis of malonyl-CoA and prevents malonyl-CoA from inhibiting CTP1, thus promoting FA uptake into the mitochondria and FA oxidation. Lastly, AMPK activation promotes PGC-1α activity, resulting in translocation of PGC-1α to the nucleus, where it functions to promote transcription of mitochondrial genes. Abbreviations: ACC, acetyl-CoA carboxylase; ACS, acyl-CoA synthetase; AMPK, AMP-activated protein kinase; CD36, fatty acid translocase; CPT1, carnitine palmitoyl transferase 1; DRP1, dynamin-related protein 1; FA, fatty acid; FABPc, fatty acid–binding protein cytosolic; FABPpm, fatty acid–binding protein plasma membrane; FATP, fatty acid transport protein; GLUT4, glucose transporter type 4; MFF, mitochondrial fission factor; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1 alpha; RAB GAP, GTPase-activating protein–bound form of RAB; RAB GDP, guanosine diphosphate–bound form of RAB; RAB GEF, guanine nucleotide exchange factor–bound form of RAB; RAB GTP, guanosine-5′-triphosphate-bound form of RAB; Ser, serine; TBC1D1, TBC1 domain family member 1; TBC1D4, TBC1 domain family member 4; Thr, threonine; ULK1, Unc-51-like autophagy activating kinase 1.

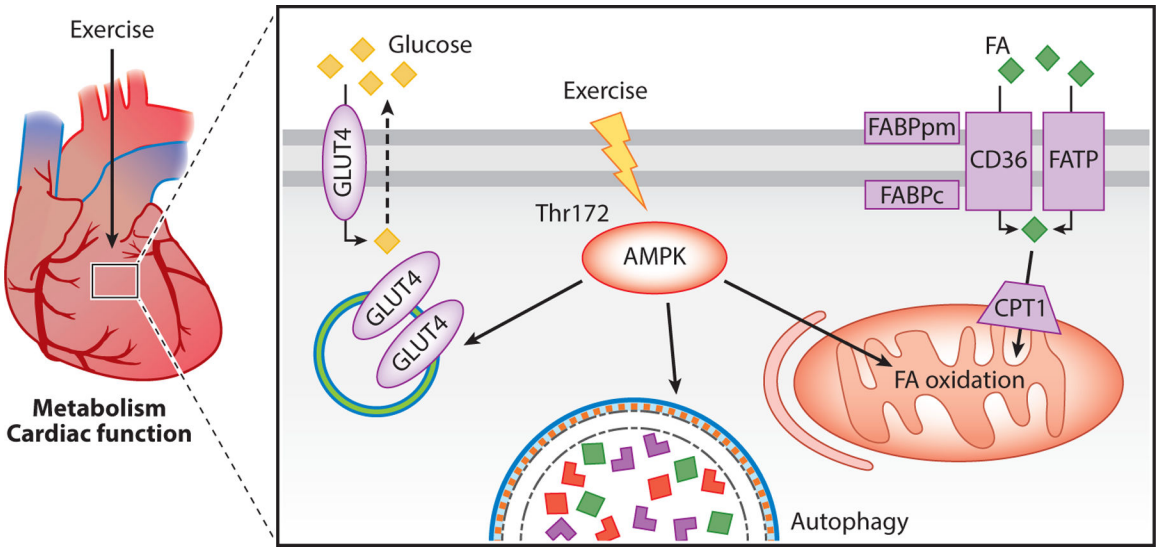

Figure 2.

Exercise-induced AMPK activation in cardiac metabolism and function. Phosphorylation of AMPK leads to increased GLUT4 mobilizing to the sarcolemma to increase glucose uptake. AMPK activation also increases autophagy and oxidation of FA. Abbreviations: AMPK, AMP-activated protein kinase; CD36, fatty acid translocase; CPT1, carnitine palmitoyl transferase 1; FA, fatty acid; FABPc, fatty acid–binding protein cytosolic; FABPpm, fatty acid–binding protein plasma membrane; FATP, fatty acid transport protein; GLUT4, glucose transporter type 4; Thr, threonine.

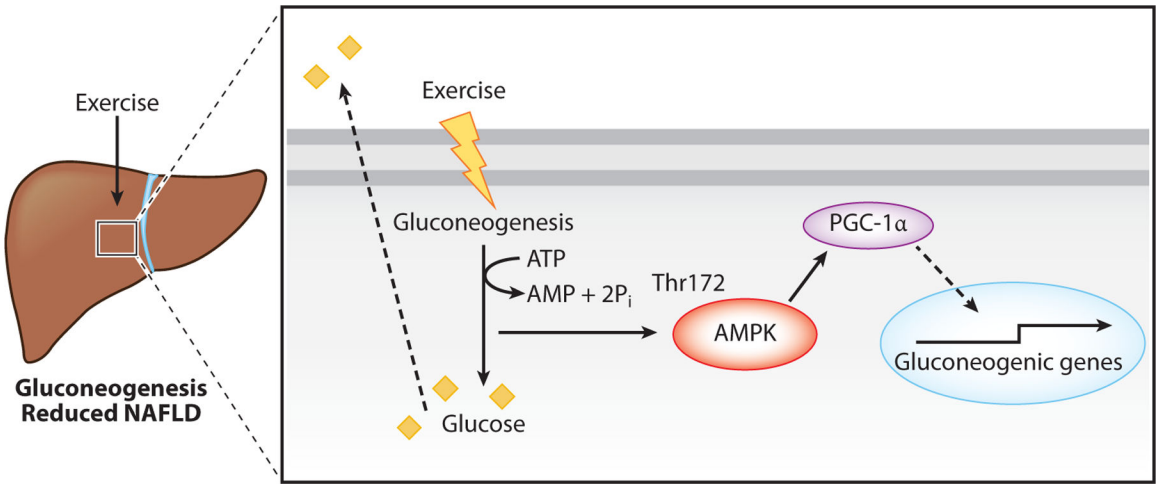

Figure 3.

Exercise and AMPK activation in hepatic gluconeogenesis. Exercise increases gluconeogenesis, leading to increased glucose for redistribution to the heart and muscle. Gluconeogenesis is an ATP-consuming process resulting in an increased AMP/ATP ratio that activates AMPK. This leads to PGC-1α activation and increased transcription of gluconeogenic genes. Abbreviations: AMPK, AMP-activated protein kinase; NAFLD, nonalcoholic fatty liver disease; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1 alpha; P_i, inorganic phosphate; Thr, threonine.

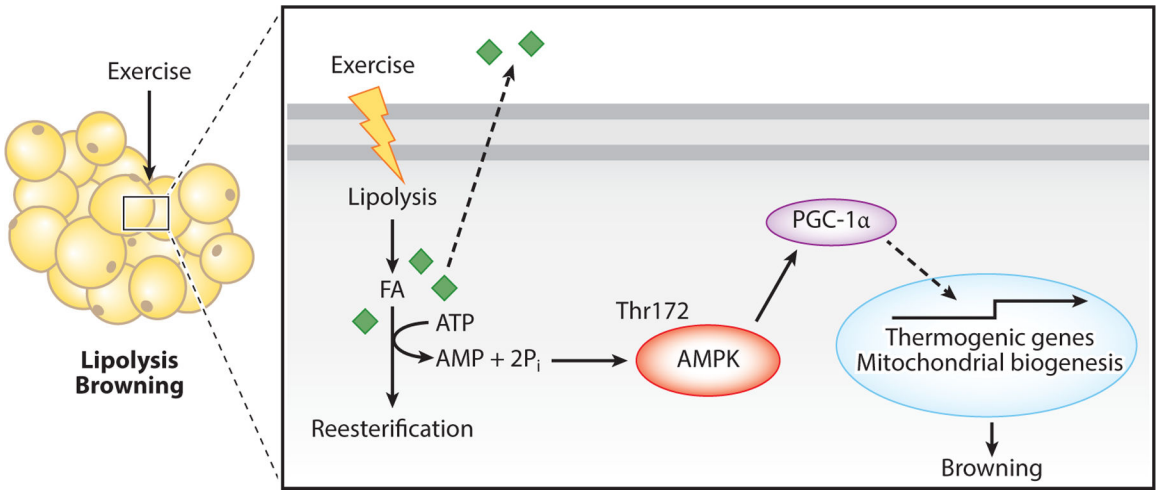

Figure 4.

Exercise and AMPK activation in lipolysis and browning of white adipose tissue. Exercise induces lipolysis, resulting in increased FA release as fuel for other tissues/organs as well as reesterification of FA into triacylglyceride. Reesterification is an ATP-consuming process resulting in increased AMPK activation and increased PGC-1α-promoted transcription of thermogenic genes and mitochondrial biogenesis. These metabolic changes lead to adipose browning. Abbreviations: AMPK, AMP-activated protein kinase; FA, fatty acid; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1 alpha; P_i, inorganic phosphate; Thr, threonine.

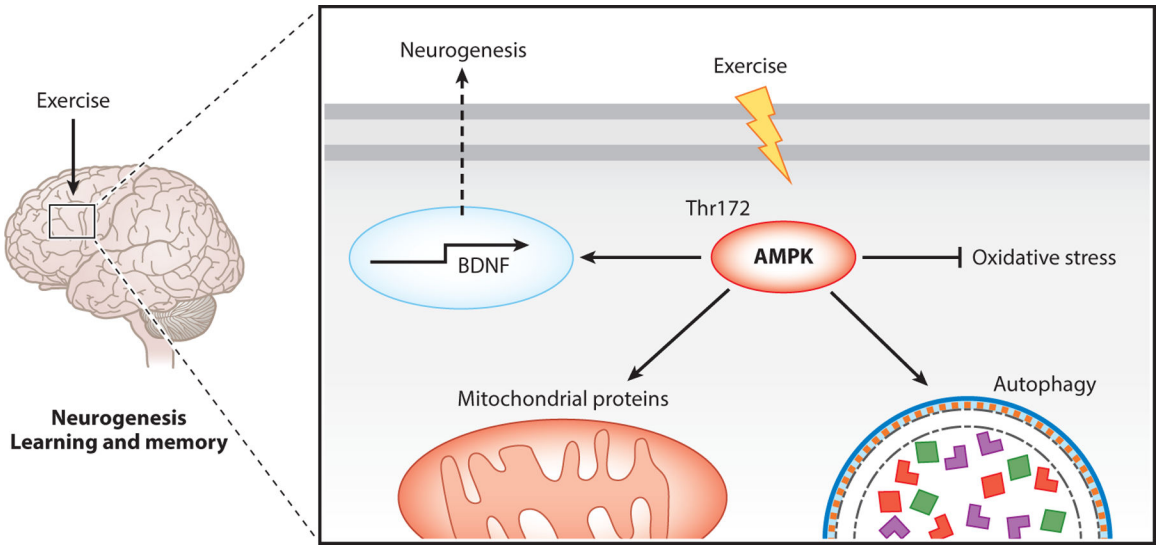

Figure 5.

Exercise-induced AMPK activation in brain adaptation and neurogenesis. Exercise increases AMPK activity, leading to increased transcription of BDNF that promotes neurogenesis. AMPK also increases mitochondria content while promoting autophagy and inhibiting oxidative stress. Abbreviations: AMPK, AMP-activated protein kinase; BDNF, brain-derived neurotrophic factor; Thr, threonine.