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LKB1 and AMPK and the regulation of skeletal muscle metabolism

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Abstract

Purpose of review—To address the role of LKB1 and AMP-activated protein kinase (AMPK) in glucose transport, fatty acid oxidation, and metabolic adaptations in skeletal muscle.

Recent findings—Contraction-mediated skeletal muscle glucose transport is decreased in muscle-specific LKB1 knockout mice, but not in whole body AMPKα2 knockout mice or AMPKα2 inactive transgenic mice.

Chronic activation of AMPK by 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (AICAR) and β-guanadinopropionic acid enhances mitochondrial function in skeletal muscle, but AICAR or exercise-induced increases in mitochondrial markers are preserved in skeletal muscles from whole body AMPKα2 or muscle-specific LKB1 knockout mice.

Pharmacological activation of AMPK increases glucose transport and fatty acid oxidation in skeletal muscle. Therefore, chronic activation of AMPK may be beneficial in the treatment of obesity and type 2 diabetes.

Summary—LKB1 and AMPK play important roles in regulating metabolism in resting and contracting skeletal muscle.

Keywords

fatty acid oxidation; glucose transport; mitochondrial biogenesis

Introduction

The AMP-activated protein kinase (AMPK) was first identified as a Ser/Thr kinase that inactivates key enzymes involved in lipid and cholesterol biosynthesis [1]. In skeletal muscle, several lines of evidence support a role of AMPK in the regulation of glucose transport. LKB1 is a Ser/Thr kinase that is thought to be a master regulator for a diverse array of cellular processes. It has been well documented that LKB1 functions in the regulation of skeletal muscle metabolic processes. Our group and others have generated mice lacking AMPK activity in skeletal muscle as well as muscle-specific LKB1 knockout mice. In this review, we discuss the potential roles of LKB1 and AMPK in regulating skeletal muscle metabolism. In particular, we discuss data pertaining to the question of whether AMPK and LKB1 are necessary for contraction-stimulated glucose transport in skeletal muscle, and whether these proteins are necessary for adaptations that occur in muscle in response to exercise training.

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Structure and regulation of AMPK

AMPK is an evolutionally conserved Ser/Thr kinase that functions in the regulation of energy metabolism [2]. In mammalian tissues, AMPK consists of heterotrimeric complexes containing a catalytic α subunit and regulatory β and γ subunits. Each subunit has two or more different isoforms [2–4]. The α1 subunit is widely expressed, whereas the α2 isoform is dominant in skeletal muscle, heart, and liver [5,6]. Phosphorylation of the Thr^{172} site on the α1 and α2 catalytic subunits by upstream kinase(s) is essential for AMPK activation [7–9]. Recent studies have shown that LKB1 [7,10,11] and Ca^{2+}/calmodulin kinase kinase (CaMKK) [12–14] can serve as upstream kinases for AMPK. Given that muscle-specific LKB1 knockout mice [15] and hypomorphic LKB1 knockout with a muscle LKB1 knockout [16] show ablated AMPKα2 activity in skeletal muscle, LKB1 appears to be a major AMPK kinase in skeletal muscle.

The AMPK β-subunit may function as a scaffold for the complex [17] and may also be an important regulator of glycogen metabolism via a glycogen-binding domain [18,19]. The γ-subunit has 4-cystathionine-β-synthase (CBS) domains. These domains are required for the binding of AMP or ATP, which increases or decreases AMPK activity, respectively [20]. Binding of AMP to the γ-subunit is thought to maintain AMPK activity by preventing dephosphorylation of the Thr^{172} site [21•].

AMPK is activated via various cellular energy stressors and signaling pathways regulating insulin sensitivity and/or glucose transport, including in vivo exercise [22,23], hypoxia [24], leptin [25], and adiponectin [26]. AMPK can be pharmacologically activated by the antidiabetic drugs metformin [27,28] and rosiglitazone [29]. AMPK activity is also increased in response to 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (AICAR), which is taken up by the cell and metabolized to ZMP, an AMP analogue [2]. The activation of AMPK results in the phosphorylation of multiple downstream substrates, whose overall effects are to increase ATP production by activating pathways involved in fatty acid oxidation and glucose transport, and to simultaneously decrease ATP consumption by inhibiting pathways that lead to fatty acid, protein, and glycogen synthesis (Fig. 1) [4,30].

Role of LKB1 and AMPK in glucose transport in skeletal muscle

Early studies from our laboratory and others provided evidence that AMPK mediates glucose transport in skeletal muscle. AICAR-induced activation of AMPK causes insulin-independent increases in skeletal muscle glucose transport [24,31]. Several studies have shown that this increase occurs concomitantly with glucose transporter 4 (GLUT4) translocation to the plasma membrane [32], similar to the effects of exercise and muscle contraction [33]. Generation of muscle-specific transgenic mice overexpressing a dominant negative form of AMPKα2, the major AMPK α subunit in skeletal muscle, and whole body knockout of AMPKα2 showed that AICAR-stimulated glucose transport was completely inhibited [34]. Collectively, these studies suggest that the activation of AMPK can lead to the activation of glucose transport in skeletal muscle. Although it is clear that AICAR-stimulated increases in skeletal muscle glucose transport are mediated by AMPKα2, there is emerging evidence that AMPK cannot be the sole mediator of contraction-stimulated glucose transport. Mu *et al.* [34] found only partial inhibition of contraction-mediated glucose transport in AMPKα2 dominant negative mice, and AMPKα1 and α2 knockout mice showed normal contraction-stimulated glucose transport [35]. Furthermore, we have generated muscle-specific AMPKα2 inactive transgenic mice and found that with normalization of force generation, there is no decrease in contraction-stimulated glucose transport in AMPKα2 inactive mice [36]. In addition, in-vivo measurements of contraction-stimulated glucose transport in multiple skeletal muscles (tibialis anterior, extensor

digitorum longus, gastrocnemius) were completely normal in AMPKα2 inactive mice [36]. These data suggest that AMPK is not essential for contraction-stimulated glucose transport in skeletal muscle. Instead, there may be multiple, potentially redundant, signaling mechanisms mediating contraction-mediated glucose transport in skeletal muscle.

To determine the potential role of the AMPK upstream kinase, LKB1, our group has generated a muscle-specific LKB1 knockout mouse (MLKB1KO) [15]. Furthermore, Sakamoto *et al.* [16] have studied a hypomorphic LKB1 mouse in which whole body LKB1 protein is decreased by 70–80% and skeletal muscle LKB1 is ablated. In contrast to results from whole body AMPK (α1 and α2) knockout mice and AMPKα2 inactive transgenic mice, contraction-stimulated glucose transport was partially inhibited in these two LKB1 knockout mouse models [16,37]. Although it is not yet clear how LKB1 regulates contraction-stimulated glucose transport in skeletal muscle, decreased glucose transport cannot be explained by inactivation of AMPKα2 alone. Instead, the decrease in glucose transport could be due to decreased activity of one or more other LKB1 substrates. LKB1 is known to phosphorylate at least 12 AMPK-related protein kinases that are similar in structure and/or function to AMPK [38,39]. Although there have been no studies on the potential function of these AMPK-related kinases in regulating glucose transport in skeletal muscle, one report suggests that only some of the AMPK-related kinases (QSK, QIK, MARK2/3, and MARK4) are expressed in rat skeletal muscle, and that none of these proteins are activated by in-situ muscle contraction [40]. Interestingly, Fisher *et al.* [41] recently demonstrated that both muscle contraction and AICAR increase phosphorylation of the AMPK-related protein kinase (ARK) 5 in rat skeletal muscle. However, the increase in ARK5 phosphorylation was not associated with elevated enzyme activity. Thus, it is likely that contraction-stimulated glucose transport is regulated by one or more alternative downstream substrates of LKB1 (Fig. 2).

Role of LKB1 and AMPK in lipid metabolism

Acute exercise results in large increases in fatty acid transport and oxidation in skeletal muscle. AMPK has been suggested to be a critical regulator of fatty acid oxidation by phosphorylating and inactivating acetyl CoA carboxylase (ACC) [22], which results in decreased production of the carnitine palmitoyltransferase I (CPT1) inhibitor, malonyl-CoA. CPT1 promotes fatty acid transport into mitochondria for subsequent oxidation [42]. Several studies [25,26,43,44] have provided evidence that AMPK activation is required for AICAR, leptin, or adiponectin-mediated fatty acid oxidation in skeletal muscle. Similarly, the effects of TNFα [45] and resistin [46] on decreased fatty acid oxidation are at least partially mediated by impaired AMPK activity in these models. Studies on mutant mice in which mutation of the γ3 subunit results in elevated AMPK activity (AMPKγ3R225) demonstrated that these mice had increased fatty acid oxidation and were protected from high fat diet-induced accumulation of intramuscular triglyceride [47]. We have found that muscle-specific LKB1 knockout mice have elevated intramuscular triglycerides [15]. Using a similar muscle-specific LKB1 knockout mouse model, Thompson *et al.* [48•] have shown impaired AICAR-induced fatty acid oxidation. Thus, LKB1 plays an important role in fatty acid oxidation, likely via activation of AMPK.

Role of LKB1 and AMPK in metabolic adaptation

The importance of chronic exercise for people with type 2 diabetes has been clearly established. Exercise training improves glucose homeostasis by enhancing skeletal muscle glucose transport and insulin action [49,50] and increases mitochondrial biogenesis [51–53]. These benefits are most likely related to a number of muscle adaptations in response to exercise training. AMPK has been proposed as a key molecule mediating these adaptations.

Initial studies [54] have shown that chronic administration of AICAR significantly increases GLUT4 and hexokinase II, which are important for glucose transport. AICAR has also been shown to have potent effects on mitochondrial markers in skeletal muscle [44] similar to the effects of exercise training [51,55–57]. This effect was independently confirmed using another approach. Mice fed β-guanadinopropionic acid, a creatine analogue that reduces the intramuscular ATP/AMP ratio and thus results in increased AMPK activity, showed increased mitochondrial biogenesis mediated by PGC-1α and NRF-1 transcription factors [58], an adaptation that was abolished in transgenic mice overexpressing a dominant negative form of AMPKα2 [59]. Finally, decreased AMPK activity in aged human participants has been associated with decreased mitochondrial function [60••]. Taken together, these data strongly suggest that AMPK is critical for metabolic adaptations in skeletal muscle. In contrast to studies using AICAR, exercise-induced increases in GLUT4, hexokinase II, and mitochondrial markers were not abolished in whole body AMPKα2 [61••] or transgenic mice overexpressing dominant negative AMPKα2 [62••], suggesting that AMPK might be an important, but not the sole pathway regulating muscle adaptation in response to exercise training.

Exercise training results in numerous adaptations to skeletal muscle, yet the initiating signal is not fully understood. Two studies [63,64] have shown that exercise training increases LKB1 protein content, concomitant with elevated expression of the transcriptional coactivator PGC1 in rat skeletal muscle [64]. This occurs despite reportedly decreased AMPK kinase activity [63,65]. In studies of muscle-specific LKB1 knockout mice [37,66••], it was shown that LKB1 is a critical regulator of exercise capacity and basal mitochondrial function. In contrast, exercise training-induced increases in GLUT4, hexokinase II, and mitochondrial markers were preserved [66••]. Therefore, LKB1-AMPK signaling is important in skeletal muscle physiology, but there must also be additional signaling pathways that regulate skeletal muscle adaptations in response to exercise training. Potential signaling molecules that may help mediate these changes include calcium/calmodulin kinase, mitogen-activated protein kinase, calcineurin, and others.

Potential therapeutical targets of AMPK and LKB1

Given that AMPK can mediate glucose transport, fatty acid oxidation, and mitochondrial biogenesis in skeletal muscle, it is likely that chronic activation of AMPK could protect individuals from developing obesity and type 2 diabetes, similar to the effects of regular physical exercise. Although the majority of studies [28,67•] demonstrate quite consistently that AMPK activity is normal in obese patients with type 2 diabetes, one recent study [67•] proposed that exercise-induced AMPK activity and phosphorylation were impaired in these groups. In animal studies [68–71], several reports demonstrate that chronic activation of AMPK by AICAR improved insulin sensitivity in various insulin resistant models such as the ob/ob mouse, fa/fa rat, and high-fat feeding models. In fact, metformin and thiazolinediones (e.g., rosiglitazone, troglitazone, and pioglitazone) are widely used drugs in the treatment of type 2 diabetes and may function via activation of AMPK. Zhou *et al.* [72] demonstrated that metformin inhibits hepatic glucose production and increases glucose transport in isolated muscle via AMPK activation. Our follow-up showed that therapeutical doses of metformin increase AMPK activity in patients with type 2 diabetes, along with improved insulin sensitivity [28]. Recently, Shaw *et al.* [73] generated liver-specific LKB1 knockout mice, which exhibit diminished liver AMPK activity. In these animals, the blood-lowering effect of metformin in knockout mice was abolished [73].

Thiazolidinediones (TZDs) are peroxisome proliferator-activated receptor γ (PPARγ) agonists that increase adiponectin secretion [74], and more recently have been found to activate muscle glucose transport mediated by AMPK [29,75]. TZDs activate AMPK in

isolated rat skeletal muscle [75]. The underlying mechanism by which these drugs activate AMPK is unclear, but may be via an inhibition of the respiratory chain, leading to an increase in the intracellular AMP/ATP ratio [29]. It is also possible that the effect of TZD administration might be due to increased secretion of adipokines such as the known AMPK activator adiponectin [76,77].

As AMPK has emerged as a promising target for treating obesity and type 2 diabetes, there has been considerable effort to develop new small molecules to activate AMPK. Recently, A-769662 was identified as a novel AMPK activator [78]. Treatment of ob/ob mice with A-769662 protected these mice from weight gain, hyperglycemia, and hyperlipidemia via a largely liver-specific mechanism.

Conclusion

Numerous studies performed over the past several years have clearly shown that activation of AMPK results in an acute increase in catabolic reactions such as glucose and fatty acid oxidation, and a rapid inhibition of anabolic processes such as lipid and cholesterol biosynthesis. Activation of AMPK is also associated with altered transcriptional regulation, which may act as an additional contributor in the long-term prevention of obesity and type 2 diabetes. Skeletal muscle LKB1, an upstream kinase of AMPK and several other AMPK-related protein kinases, has been shown to regulate contraction-stimulated glucose transport. The underlying mechanisms, which appear to be AMPK-independent, still need to be elucidated. In addition, the question whether LKB1 is useful as a therapeutical target for the treatment of type 2 diabetes is not clear as the role of LKB1 in other tissues such as adipocytes or pancreas has not been studied. AMPK activation using a novel small molecule results in improved glucose homeostasis, which is an important clinical component in treating type 2 diabetes. Recent findings suggest that chronic activation of AMPK may assist in preventing obesity and type 2 diabetes.

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•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 339–340).

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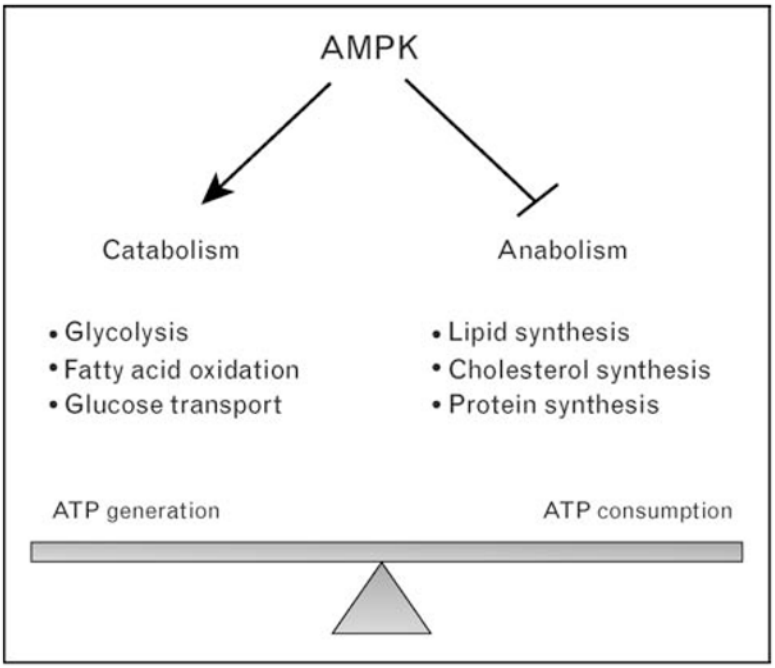

Figure 1. Activation of AMPK and metabolic consequences

AMPK activation increases catabolic reactions, which generate ATP and inhibits anabolic reactions, which consume ATP.

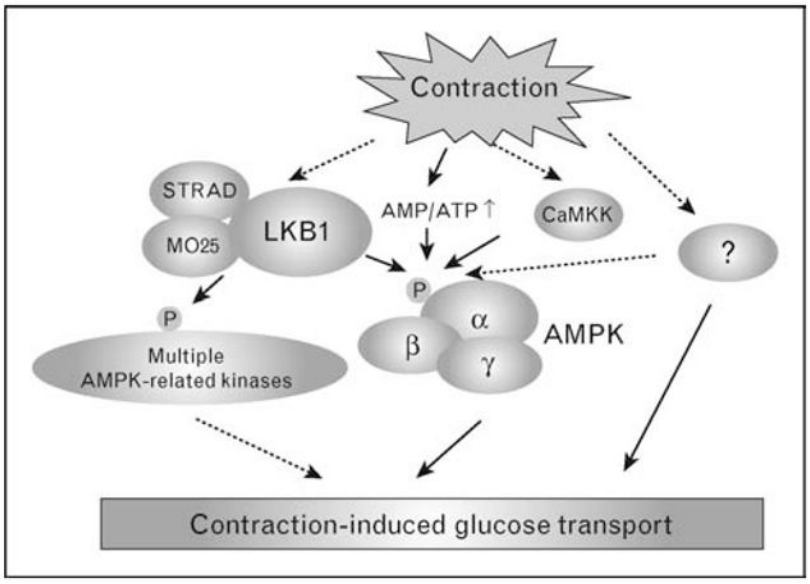

Figure 2. Schematic illustration of the pathways which are thought to regulate contraction-stimulated glucose transport in skeletal muscle

Contraction increases the [AMP]/[ATP] ratio, activates AMPK, and subsequently induces glucose transport. Studies using muscle-specifc LKB1 knockout, whole body AMPKα2 knockout, and AMPKα2 inactive transgenic mice suggest that there may be multiple pathways involved in contraction-stimulated glucose transport. Solid arrows illustrate established relationships, and dashed arrows indicate putative interactions. CaMKK, Ca^{2+}/calmodulin kinase kinase.