Postprint: The Regulatory Role of AMP-Activated Protein Kinase in Animal Glucose and Lipid Metabolism

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Abstract

AMP-activated protein kinase (AMPK) is widely expressed in eukaryotic cells. The activity of AMPK is regulated by the ratio of adenosine monophosphate (AMP) to adenosine triphosphate (ATP). Stress responses can activate AMPK by reducing ATP production or increasing ATP consumption, which elevates the intracellular AMP/ATP ratio. Activated AMPK phosphorylates downstream target proteins, altering lipid and carbohydrate metabolism to inhibit ATP-consuming processes and promote ATP-generating reactions—that is, inhibiting fatty acid and glycogen synthesis while promoting fatty acid oxidation and glucose uptake—thereby rapidly restoring cellular energy levels. Consequently, AMPK is referred to as a "cellular energy regulator" and plays a vital role in animal adaptation to environmental changes. This review summarizes the structure, distribution, activity regulation of AMPK, and its regulatory effects on glucose and lipid metabolism based on existing literature from domestic and international sources.

Full Text

Regulatory Effects of Adenosine Monophosphate-Activated Protein Kinase on Glucose and Lipid Metabolism in Animals

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Abstract: Adenosine monophosphate-activated protein kinase (AMPK) is ubiquitously expressed in eukaryotic cells. AMPK activity is regulated by the adenosine monophosphate (AMP)/adenosine triphosphate (ATP) ratio.

Stress responses that reduce ATP production or increase ATP consumption lead to elevated intracellular AMP/ATP levels, thereby activating AMPK. Once activated, AMPK phosphorylates downstream target proteins, altering lipid and carbohydrate metabolism to favor ATP-producing processes while inhibiting ATP-consuming pathways—specifically, it suppresses fatty acid and glycogen synthesis while promoting fatty acid oxidation and glucose uptake, thereby rapidly restoring cellular energy levels. Consequently, AMPK is referred to as the "cellular energy regulator" and plays a crucial role in animal adaptation to environmental changes. This review summarizes the structure, distribution, activity regulation, and regulatory roles of AMPK in glucose and lipid metabolism based on existing literature.

Key words: AMPK; animal; glucose metabolism; lipid metabolism

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The effectiveness and coordination of metabolic regulation are crucial mechanisms for animals to adapt to environmental changes, while disturbances in glucose and lipid metabolism can lead to a series of metabolic syndrome clusters. When nutrient intake exceeds energy utilization, the surplus energy is stored as fat and glycogen, causing excessive fat accumulation and metabolic disorders. Adenosine monophosphate-activated protein kinase (AMPK), a member of the serine kinase family, is expressed in various organs as a multi-subunit enzyme highly sensitive to cellular energy status. It regulates the direction of metabolic energy production and consumption based on cellular energy states, playing a pivotal role in controlling intracellular energy flow [1]. AMPK functions not only as an energy sensor at the cellular level but also participates in regulating whole-body energy expenditure and intake through hormones and cytokines such as leptin and adiponectin, making it central to research on diabetes, non-alcoholic fatty liver disease, and other metabolism-related disorders [2]. In recent years, due to the global epidemic of obesity, diabetes, and metabolic syndrome, the role of AMPK in glucose and lipid metabolism has attracted widespread attention, becoming a hotspot in biochemistry and biomedicine. This review summarizes research progress on AMPK, provides an overview and analysis of its functions in glucose and lipid metabolism, and offers new research perspectives for addressing stress and nutritional metabolic diseases in animal production.

1. Molecular Structure and Distribution Characteristics of AMPK

AMPK is a heterotrimeric protein composed of three subunits: , , and . The subunit serves as the catalytic subunit with a molecular mass of 63 kDa and contains two functional domains: an N-terminal catalytic core and a C-terminal region responsible for binding to and subunits and regulating AMPK activity [3]. The and subunits are regulatory subunits with molecular masses of 38 kDa and 35 kDa, respectively. These subunits play crucial roles in maintaining AMPK stability and substrate specificity; the subunit mediates AMPK bind-

ing to glycogen on membranes, while the subunit is responsible for binding adenosine monophosphate (AMP). AMPK activity requires co-expression of all three subunits [4].

The three AMPK subunits each have distinct isoforms. The subunit has two isoforms, 1 and 2. 1 is widely distributed in liver, lung, kidney, testis, and brain, whereas 2 is predominantly expressed in liver, skeletal muscle, and cardiac muscle. 2 exhibits stronger AMP dependence, while 1 shows greater resistance to dephosphorylation by protein phosphatase 2A (PP2A). These differences likely arise from variations in AMPK subunit composition across tissues and differential substrate specificity [5]. The subunit has two isoforms, 1 and 2; 1 is primarily found in rat liver, while 2 is abundantly expressed in skeletal and cardiac muscle. The subunit has three known isoforms: 1, 2, and 3. 1 and 2 are broadly distributed across most tissues and organs, whereas 3 is mainly expressed in skeletal muscle. 2 shows strong AMP dependence and may be involved in AMP binding.

2. Regulation of AMPK Activity

2.1 Regulation via the AMP/ATP Ratio

In animals, AMPK activity is primarily regulated by cellular energy status, specifically through the AMP/ATP ratio. When energy expenditure depletes ATP and elevates AMP levels, AMPK activity increases, shifting metabolism toward ATP production and inhibiting ATP consumption to maintain cellular energy homeostasis [1].

Under physiological conditions, cells maintain high ATP concentrations to support basic metabolic needs. Studies have identified AMP as a specific AMPK activator that functions both as an allosteric activator and influences AMPK phosphorylation by AMPK kinase (AMPKK), though the exact mechanisms remain unclear. Subsequent research revealed four distinct roles of AMP: (1) direct allosteric activation of AMPK; (2) binding to dephosphorylated AMPK to create a better substrate for AMPKK; (3) binding to phosphorylated AMPK to make it a poorer substrate for protein phosphatase 2C (PP2C); and (4) direct activation of AMPKK.

AMPK exists in two conformations: an active R state and an inactive T state, and in two phosphorylation forms: phosphorylated and non-phosphorylated AMPK. These combine to form four possible states [T, R, T(P), and R(P)]. Only in the R conformation can AMPKK phosphorylate non-phosphorylated AMPK, while only the T(P) conformation allows dephosphorylation of phosphorylated AMPK. However, AMP’ s effects are inhibited by high ATP concentrations, which suppress both allosteric activation and phosphorylation of AMPK by AMP, and can also inhibit AMPK activation through AMPKK. Therefore, AMPK activity is regulated by the AMP/ATP ratio rather than by AMP alone.

AMPK can be activated by various cellular stresses that deplete ATP, includ-

ing metabolic poisons such as tricarboxylic acid cycle inhibitors (arsenite), respiratory chain inhibitors (antimycin A, azide), mitochondrial ATP synthase inhibitors (oligomycin), and oxidative phosphorylation uncouplers like dinitrophenol [6-7]. AMPK is also activated by pathological stresses including glucose deficiency, ischemia, hypoxia, and oxidative stress [8]. All these stimuli increase the AMP/ATP ratio, thereby activating AMPK.

Under normal physiological conditions, AMPK activation occurs through skeletal muscle exercise or contraction. The degree of AMPK activation depends on exercise intensity and is thought to be induced by changes in the AMP/ATP ratio. Activated AMPK inhibits ATP consumption while activating carbohydrate and fatty acid metabolism to restore ATP levels in muscle.

2.2 Regulation via AMP-Independent Pathways

Studies have found that the type 2 diabetes drugs metformin and thiazolidinediones can activate AMPK. While thiazolidinediones activate AMPK in an AMP-dependent manner by increasing the AMP/ATP ratio, metformin activates AMPK independently of AMP without altering the AMP/ATP ratio [8]. Hawley et al. [9] demonstrated that metformin activates AMPK by increasing phosphorylation of threonine (Thr) 172 in the catalytic subunit.

Recent studies have shown that AMPK also partially mediates the lipid-lowering effects of leptin, adiponectin, and epinephrine. Leptin, an adipocyte-secreted hormone that regulates food intake and energy expenditure, also plays a key role in neuroendocrine function. Research indicates that leptin selectively stimulates activation and phosphorylation of the AMPK 2 subunit in skeletal muscle, exerting dual effects on AMPK activation: early activation at the muscle level followed by later inhibition through the hypothalamic-sympathetic nervous system axis, leading to reduced food intake and body weight [10]. Adiponectin, another adipocyte-secreted factor, plays important roles in macromolecular complex cycling, increased fatty acid oxidation and glucose uptake, and inhibition of gluconeogenesis [11]. Adiponectin promotes AMPK phosphorylation and activation both in vivo and in vitro, though the specific mechanism remains unclear.

5-aminoimidazole-4-carboxamide riboside (AICAR), an intermediate in inosine monophosphate production, is readily taken up by cells and rapidly phosphorylated to its mononucleotide derivative (ZMP), which activates AMPK similarly to AMP. AICAR activation of AMPK does not affect AMP, ADP, or ATP concentrations. Systematic studies comparing AMP and ZMP revealed that both produce maximal activation effects, influence specific product saturation curves identically, and bind to the same allosteric site, demonstrating additive and competitive effects [12]. Unlike AMP, which has a short metabolic half-life in cells, ZMP can maintain stable intracellular concentrations for extended periods, making AICAR widely used as a specific AMPK activator.

To date, knowledge of AMPK kinase (AMPKK), the upstream kinase of AMPK, remains limited in experimental animals. AMPKK is known to be a

polypeptide similar in size to AMPK with a molecular mass of 58 kDa. Unlike AMPK, AMPKK activity is insensitive to various protein phosphatases, and no phosphorylation-dependent regulation has been identified. Studies have shown that AMPKK can phosphorylate Thr172 in the AMPK subunit, though the specific mechanism remains unclear. Recently, the tumor suppressor kinase LKB1 was found to activate AMPK by phosphorylating Thr172 in the subunit through a mechanism similar to AMPKK. Research demonstrates that AMPK activity is significantly reduced in LKB1-deficient cells compared to cells with normal LKB1 expression [13]. However, LKB1 activity is not directly regulated by stimuli that activate AMPK, nor is it directly activated by AMP.

Studies have shown that LKB1 can activate AMPK by phosphorylating Thr172, establishing LKB1 as an upstream kinase of AMPK. In LKB1-deficient mouse embryonic fibroblasts subjected to various stress stimuli, phosphorylation of Thr172 and downstream AMPK signaling are almost completely abolished, leading to extensive investigation of LKB1 as an upstream regulator of AMPK [14].

Compound C is a specific inhibitor of AICAR-induced AMPK phosphorylation that blocks the anti-lipolytic effects of AICAR in rat adipocytes. Additionally, compound C inhibits ACC phosphorylation induced by both AICAR and metformin. Studies have demonstrated that compound C can suppress AICAR-induced reductions in food intake and body weight [15]. Xu et al. [16] found that intracerebroventricular injection of compound C significantly decreased food intake in chicks, leading to its widespread use as a specific AMPK inhibitor.

3. Regulatory Effects of AMPK on Metabolism

3.1 Effects on Lipid Metabolism

AMPK is a key regulator of energy metabolism in animals. Upon activation, AMPK inhibits ATP-consuming anabolic processes such as fatty acid synthesis while initiating ATP-producing catabolic processes like fatty acid oxidation, thereby maintaining energy metabolic balance. Consequently, AMPK is termed the "cellular energy regulator."

Studies have shown that activated AMPK regulates glucose and lipid metabolism in multiple tissues and organs. In the brain, a central organ, AMPK controls food intake; in skeletal muscle, it regulates fatty acid oxidation and glucose uptake to modulate energy expenditure; in liver, activated AMPK promotes fatty acid oxidation while inhibiting lipogenesis; additionally, activated AMPK suppresses insulin secretion in pancreatic islets [4]. Hormonal regulation of AMPK is illustrated in Figure 2 [Figure 2: see original paper].

Green arrow indicates stimulation/activation of AMPK; red oval indicates inhibition/deactivation.

3.1.1 Regulation via ACC ACC is a key enzyme regulating fatty acid synthesis. It exists primarily as two isoforms, ACC- and ACC- , with distinct

tissue distributions. Liver, brown adipose tissue, and brain contain both ACC- and ACC- isoforms, while skeletal and cardiac muscle predominantly express ACC- , and white adipose tissue mainly expresses ACC- .

The two ACC isoforms serve different functions: ACC- catalyzes the production of malonyl-CoA and primarily participates in fatty acid synthesis, whereas ACC- catalyzes the carboxylation of acetyl-CoA to malonyl-CoA, which allosterically inhibits carnitine palmitoyltransferase 1 (CPT1) activity, thereby regulating fatty acid oxidation [17].

Early studies purifying ACC peptides from lactating rat mammary glands revealed that AMPK phosphorylates ACC at three sites: serine (Ser) 79, Ser1200, and Ser1215, with Ser79 having the greatest impact on ACC activity [18]. Recent research shows that cellular stress and treatment with the AMPK-specific activator AICAR increase AMPK activity in rat hepatocytes, leading to ACC- phosphorylation and inactivation, thereby inhibiting fatty acid synthesis [19]. In vivo experiments have similarly demonstrated that activated AMPK phosphorylates and reduces ACC activity [20].

Fatty acid synthase (FAS) is a multifunctional enzyme found in lipogenic tissues such as liver and adipose tissue that catalyzes the synthesis of long-chain fatty acids (primarily palmitic acid) using acetyl-CoA and malonyl-CoA as substrates, playing a crucial role in fatty acid synthesis. Foretz et al. [21] and Kamikubo et al. [22] found that AMPK participates in regulating FAS gene expression, with activated AMPK inhibiting glucose-stimulated transcription.

3.1.2 Regulation via HMGR HMGR is an AMPK substrate that primarily regulates cholesterol synthesis and was the first identified AMPK substrate. Current research shows that AMPK inhibits HMGR catalytic activity by phosphorylating Ser871 in the HMGR peptide chain. During ATP consumption, HMGR activity decreases, and transfection studies revealed that mutation of HMGR at Ser871 renders it insensitive to AMPK activation during ATP depletion [23].

Some studies have found that phosphorylated Ser871 does not affect HMGR turnover in vivo, and that post-transcriptional feedback downregulation of HMGR Ser871 mutants remains normal when cells are incubated with mevalonate, 25-hydroxycholesterol, or low-density lipoprotein (LDL).

Li et al. [24] found that AMPK expression decreases while HMGR expression increases in steatotic cells. The finding that adiponectin activates AMPK and reduces cholesterol synthesis in apolipoprotein E (ApoE)-deficient mice suggests that hormonal regulation of HMGR through AMPK may be key to controlling cholesterol metabolism [25]. Studies show that during mild heat stress, AMPK is partially activated, partially inhibiting fatty acid synthesis but not cholesterol synthesis; however, during severe heat stress, AMPK activation is robust and inhibits both fatty acid and cholesterol synthesis, indicating that HMGR is less sensitive to AMPK activity changes than ACC [19].

3.1.3 Regulation via HSL HSL is the enzyme responsible for hydrolyzing acylglycerols and cholesterol esters in animals. Although researchers identified adipose tissue sensitivity to catabolic stimuli decades ago, hormone-sensitive lipase was only recently purified from rat epididymal fat pads.

Studies have shown that cAMP-elevating agents (e.g., epinephrine, glucagon) stimulate HSL phosphorylation at Ser563 via cAMP-dependent protein kinase, promoting lipolysis. However, AMPK phosphorylates HSL at a nearby site (Ser565), which, while not directly affecting HSL activity, completely inhibits cAMP-dependent protein kinase-mediated phosphorylation and activation. Thus, cAMP-dependent protein kinase promotes HSL phosphorylation at Ser563, whereas AMPK inhibits it at Ser565, demonstrating opposing functions for these two sites [26]. When AMPK phosphorylates HSL at Ser565, Ser563 can no longer be phosphorylated by PKA, thereby suppressing lipid breakdown. Roepstorff et al. [27] found that exercise increases AMPK 2 activity in skeletal muscle, inhibiting HSL activity and consequently suppressing fat decomposition.

3.1.4 Regulation via GPAT Studies have identified GPAT as a key enzyme in fatty acid acylation and triglyceride synthesis. Hammond et al. [28] found that GPAT-deficient mice exhibit reduced body weight, decreased adipose tissue content, and lower hepatic TG levels, whereas GPAT-overexpressing mice show reduced fatty acid oxidation and enhanced TG esterification.

Deborah et al. [29] added AICAR to cultured rat hepatocytes and found that mitochondrial GPAT activity decreased by 29-43% after 60 minutes of culture. After 90 minutes, the incorporation of [3H]glycerol and [14C]oleic acid into triglycerides decreased by 38% and 50%, respectively, while [14C] incorporation into diglycerides decreased by 60%.

Saha et al. [30] found that low-dose AICAR administration to rats reduced GPAT activity, suggesting that changes in GPAT activity may be mediated by AMPK.

Muoio et al. [31] discovered that both CPT1 and GPAT are located on the mitochondrial outer membrane, and their activities may determine the metabolic fate of acyl-CoA. AMPK-mediated GPAT inactivation not only suppresses fatty acid synthesis but also promotes fatty acid oxidation by reducing GPAT's ability to compete with CPT1 for acyl-CoA.

3.1.5 Promotion of Fatty Acid Oxidation Studies have shown that AMPK regulates fatty acid oxidation through the AMPK-ACC-malonyl-CoA-CPT1 pathway. CPT1 transports long-chain fatty acids from carnitine into mitochondria for -oxidation. Malonyl-CoA is a physiological inhibitor of CPT1 that regulates fatty acid oxidation; under normal physiological conditions, high cellular malonyl-CoA levels allosterically inhibit CPT1, thereby reducing fatty acid oxidation [32].

When the organism is stressed or treated with AMPK activators, AMPK activity increases, inhibiting ACC activity and reducing malonyl-CoA levels. This alleviates allosteric inhibition of CPT1, promoting mitochondrial fatty acid - oxidation. Studies have shown that treating cultured human umbilical vein endothelial cells with AICAR for 2 hours increases AMPK activity, decreases ACC activity, reduces malonyl-CoA concentration, and elevates palmitate oxidation [33].

Tan et al. [34] found that high-fat diet feeding decreased AMPK activity and increased ACC activity in mice. Atkinson et al. [35] reported that ACC- knockout mice exhibited increased food intake but reduced body fat content, indicating that ACC- deletion accelerates fatty acid oxidation and decreases fat accumulation.

3.2 Effects on Glucose Metabolism

3.2.1 Promotion of Glucose Uptake Studies have found that both muscle contraction and AICAR stimulation increase AMPK activity in rat skeletal muscle and promote glucose uptake by muscle cells, though through a mechanism distinct from insulin. Insulin primarily promotes glucose uptake by activating phosphatidylinositol-3-kinase (PI3K); however, PI3K inhibitors can block insulin action, and insulin resistance disrupts glucose uptake [36].

Winder et al. [37] found that AICAR treatment of rat cardiomyocytes enhances glucose uptake in a manner unaffected by PI3K inhibition but suppressible by AMPK inhibitors.

Studies have demonstrated that AICAR promotes translocation of glucose transporter 4 (GLUT4) from the cytoplasm to the plasma membrane, confirming that AMPK' s effects involve GLUT4.

3.2.2 Inhibition of Glycogen Synthesis The role of AMPK in glycogen metabolism regulation has been extensively studied. Research shows that AMPK phosphorylates glycogen synthase (GS) at Ser7, thereby inhibiting its activity [38]. Several years later, Young et al. [39] further demonstrated AMPK' s role in glycogen metabolism, showing that AMPK activation by AICAR in rat muscle cells increases glycogen phosphorylase (GP) activity.

Vincent et al. [40] cultured rat hepatocytes in vitro and found that adding 100 mol/L AICAR to the culture medium reduced glucose production by 50%, while 500 mol/L AICAR completely inhibited glucose production, demonstrating that AMPK can suppress glucose synthesis.

Wang et al. [41] found that dietary supplementation with AMPK inhibitors suppressed glycogen synthase activity and significantly reduced hepatic glycogen content.

Conclusion

AMPK is an adenosine monophosphate-activated protein kinase that serves as a central component of the protein kinase cascade system and acts as an intracellular energy sensor, regulating metabolic status in various peripheral tissues including liver and hypothalamus. Activated AMPK inhibits fat and glycogen synthesis while promoting fatty acid oxidation and glucose uptake, exerting significant ameliorative effects on insulin resistance and diabetes. Existing research has demonstrated that AMPK mediates metabolic regulation in major glucose and lipid metabolic tissues. Although studies in experimental animals or human medicine may not be directly applicable to livestock, AMPK research findings may provide new insights for addressing issues in animal production. As AMPK research continues to deepen, elucidating its role in nutritional metabolic diseases will be of paramount importance.

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