Postprint: Regulation of Animal Glucose and Lipid Metabolism by AMP-Activated Protein Kinase

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Abstract

AMP-activated protein kinase (AMPK) is ubiquitously expressed in eukaryotic cells. The activity of AMPK is regulated by the adenosine monophosphate (AMP)/adenosine triphosphate (ATP) ratio. Stress responses can activate AMPK by reducing ATP production or increasing its consumption, thereby elevating intracellular AMP/ATP levels. Activated AMPK phosphorylates downstream target proteins, thereby altering lipid and carbohydrate metabolism to inhibit ATP-consuming processes and promote ATP-generating reactions. Specifically, it suppresses fatty acid and glycogen synthesis while promoting fatty acid oxidation and glucose uptake, thus rapidly restoring cellular energy homeostasis. Therefore, AMPK is referred to as the "cellular energy regulator" and plays a vital role in animal adaptation to environmental changes. Based on existing domestic and international literature, this article provides a comprehensive review of AMPK structure, distribution, activity regulation, and its modulatory effects on glucose and lipid metabolism.

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 can decrease ATP production or increase ATP consumption, leading to elevated intracellular AMP/ATP levels that activate AMPK. Once activated, AMPK phosphorylates downstream target proteins, redirecting lipid and carbohydrate metabolism toward inhibiting ATP-consuming processes while promoting ATP-generating reactions. Specifically, AMPK suppresses fatty acid and glycogen synthesis while enhancing fatty acid oxidation and glucose uptake, thereby rapidly restoring cellular energy levels. Consequently, AMPK is termed the "cellular energy regulator" and plays a crucial role in animal adaptation to environmental changes. This review summarizes the structure, distribution, activity regulation, and modulatory effects on glucose and lipid metabolism of AMPK based on existing literature.

Keywords: AMPK; animal; glucose metabolism; lipid metabolism

The effectiveness and coordination of metabolic regulation are essential mechanisms for animals to adapt to environmental changes, while disturbances in glucose and lipid metabolism can trigger a series of metabolic syndrome manifestations. When nutrient intake exceeds energy utilization, the surplus is stored as fat and glycogen, leading to excessive fat accumulation and metabolic disorders. As a member of the serine kinase family, AMPK is expressed in various organs and represents a highly sensitive multi-subunit enzyme that modulates the direction of metabolic energy production and consumption according to cellular energy status, thereby playing a pivotal role in controlling intracellular energy flow. AMPK functions not only as a cellular energy sensor 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. 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 biomedical research. This article reviews and analyzes the research progress on AMPK' s role in glucose and lipid metabolism, offering new perspectives for studying stress and nutritional metabolic diseases in animal production.

1 Molecular Structure and Distribution Characteristics of AMPK

AMPK is a heterotrimeric protein composed of α, β, and γ subunits. The α 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 the β and γ subunits and regulating AMPK activity. The β and γ subunits are regulatory subunits with molecular masses of

38 kDa and 35 kDa, respectively. These subunits play important roles in maintaining AMPK stability and substrate specificity, with the β subunit mediating AMPK binding to glycogen on membranes and the γ subunit responsible for binding AMP. Full AMPK activity requires co-expression of all three subunits.

Each of the three subunits has distinct isoforms. The α subunit exists as two isoforms, $ $1 and $ $2. $ $1 is widely distributed in the liver, lungs, kidneys, testes, and brain, whereas $ $2 is primarily found in the liver, skeletal muscle, and cardiac muscle. $ $2 exhibits stronger AMP dependence, while $ $1 shows strong resistance to dephosphorylation by protein phosphatase 2A (PP2A). These differences likely arise from variations in AMPK subunit composition across tissues and differential substrate specificity. The β subunit has two isoforms, $ $1 and $ $2, with $ $1 predominantly present in rat liver and $ $2 highly expressed in skeletal and cardiac muscle. The γ subunit has three known isoforms: $ $1, $ $2, and $ $3. $ $1 and $ $2 are widely distributed across most tissues and organs, while $ $3 is mainly expressed in skeletal muscle. $ $2 shows strong AMP dependence and may participate in AMP binding.

2.1 Regulation via AMP/ATP Ratio

In animals, AMPK activity is primarily regulated by cellular energy status, specifically through the AMP/ATP ratio. When energy depletion reduces ATP levels and elevates AMP levels, AMPK activity increases, redirecting metabolism toward ATP production and inhibiting ATP consumption to maintain cellular energy homeostasis.

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 precise mechanism remains unclear. Subsequent research revealed four distinct roles for 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. The regulatory model of AMP on AMPK activity is illustrated in [Figure 1: see original paper]. AMPK exists in two conformations: the active R state and inactive T state, and in two phosphorylation forms: phosphorylated and non-phosphorylated AMPK. These combine to create four configurations [T, R, T(P), and R(P)]. Only the R conformation allows AMPKK to phosphorylate non-phosphorylated AMPK, while only the T(P) conformation permits dephosphorylation of phosphorylated AMPK.

However, AMP' s effects are inhibited by high ATP concentrations, which suppress AMPK allosteric activation and phosphorylation while also inhibiting 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 stressors 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. AMPK is also activated by pathological stresses including glucose deprivation, ischemia, hypoxia, and oxidative stress. All these stimuli increase the AMP/ATP ratio, thereby activating AMPK.

Under normal physiological conditions, AMPK activation occurs through skeletal muscle exercise or contraction, with the degree of activation depending on exercise intensity and being 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

Research has shown 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. Hawley et al. found that metformin activates AMPK by increasing phosphorylation of threonine (Thr) 172 in the catalytic α subunit.

Recent studies have also revealed that AMPK partially mediates the lipid-lowering effects of leptin, adiponectin, and epinephrine. Leptin, an adipocyte-secreted hormone that regulates food intake and energy expenditure, plays a key role in neuroendocrine function. Research demonstrates that leptin selectively stimulates activation and phosphorylation of the AMPK $ $2 subunit in skeletal muscle through dual effects: early activation of AMPK at the muscle level, followed by later inhibition of AMPK activity via the hypothalamic-sympathetic nervous system axis, resulting in reduced food intake and body weight. Adiponectin, another adipocyte-secreted factor, circulates in large molecular complexes and plays important roles in increasing fatty acid oxidation and glucose uptake while inhibiting gluconeogenesis. 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 generation, is taken up by cells and rapidly phosphorylated to the mononucleotide derivative ZMP, which activates AMPK similarly to AMP. Systematic studies comparing AMP and ZMP revealed that both produce identical maximal activation effects, influence specific product saturation curves, and bind at the same allosteric site, demonstrating additive and competitive effects. 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.

Knowledge about upstream AMPK kinase (AMPKK) in experimental animals remains limited. AMPKK is known to be a polypeptide similar in size to AMPK

with a molecular mass of 58 kDa, differing from AMPK in that its activity is insensitive to various protein phosphatases and is not regulated by phosphorylation. Studies have shown that AMPKK can phosphorylate Thr172 in AMPK's α subunit, though the specific mechanism remains unclear. Recently, the tumor suppressor kinase LKB1 was found to catalyze Thr172 phosphorylation in AMPKα, activating AMPK through a mechanism similar to AMPKK. In LKB1-deficient cells, AMPK activity is significantly reduced compared to normal cells. However, LKB1 activity is not directly regulated by stimuli that activate AMPK nor is it directly activated by AMP.

Research demonstrates that LKB1 activates AMPK by phosphorylating Thr172, suggesting LKB1 functions as an upstream kinase. In LKB1-deficient mouse embryonic fibroblasts, phosphorylation at Thr172 and downstream AMPK signaling nearly completely disappear under various stress stimuli, establishing LKB1 as a key upstream factor for AMPK.

Compound C is a specific inhibitor of AICAR-induced AMPK phosphorylation that blocks the anti-lipolytic effects of AICAR in rat adipocytes and inhibits AICAR- and metformin-induced phosphorylation of acetyl-CoA carboxylase (ACC). Studies show that compound C can inhibit AICAR-induced reductions in food intake and body weight. Xu et al. found that intracerebroventricular injection of compound C in chicks significantly decreased feed intake, making compound C widely used as a specific AMPK inhibitor.

3.1 Effects of AMPK on Lipid Metabolism

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

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 control energy expenditure; in the liver, activated AMPK promotes fatty acid oxidation while inhibiting lipogenesis; and in pancreatic islets, it suppresses insulin secretion. The hormonal regulation of AMPK is illustrated in [Figure 2: see original paper].

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

3.1.1 Regulation of Fatty Acid Synthesis via ACC Acetyl-CoA carboxylase (ACC) is the key enzyme regulating fatty acid synthesis. ACC exists primarily as two isoforms, ACC-α and ACC-β, with different tissue distributions. The liver, brown adipose tissue, and brain contain both isoforms, while skeletal and cardiac muscle mainly contain ACC-β and white adipose tissue predominantly expresses ACC-α. These isoforms serve distinct functions: ACC-α

catalyzes malonyl-CoA production for fatty acid synthesis, whereas ACC-β catalyzes acetyl-CoA carboxylation to malonyl-CoA, which allosterically inhibits carnitine palmitoyltransferase-1 (CPT1) to regulate fatty acid oxidation. Early studies on ACC purified from lactating rat mammary glands identified three phosphorylation sites by AMPK: serine (Ser) 79, Ser1200, and Ser1215, with Ser79 having the greatest impact on ACC activity. Recent research shows that cellular stress and AMPK-specific activators like AICAR increase AMPK activity in rat hepatocytes, leading to ACC-α phosphorylation and inactivation, thereby suppressing fatty acid synthesis. In vivo studies confirm that activated AMPK phosphorylates and reduces ACC activity.

Fatty acid synthase (FAS), a multifunctional enzyme found in lipogenic tissues such as liver and adipose tissue, catalyzes long-chain fatty acid (primarily palmitate) synthesis using acetyl-CoA and malonyl-CoA as substrates. Foretz et al. and Kamikubo et al. demonstrated that AMPK participates in regulating FAS gene expression, with AMPK activation inhibiting glucose-stimulated transcription.

3.1.2 Regulation of Cholesterol Synthesis via HMG-CoA Reductase (HMGR) HMGR, the first identified AMPK substrate, regulates cholesterol synthesis. AMPK inhibits HMGR catalytic activity by phosphorylating Ser871 in the HMGR peptide chain. During ATP depletion, HMGR activity decreases, and transfection studies show that mutation of HMGR' s Ser871 site renders it insensitive to AMPK activation during ATP consumption. However, phosphorylated Ser871 appears non-essential for HMGR function in vivo, and 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. found decreased AMPKα expression and increased HMGR expression in steatotic cells. Adiponectin activates AMPK and reduces cholesterol synthesis in apolipoprotein E (ApoE)-deficient mice, suggesting HMGR regulation through AMPK may be key to controlling cholesterol metabolism. Studies show that mild heat stress partially activates AMPK and inhibits fatty acid synthesis without affecting cholesterol synthesis, whereas severe heat stress strongly activates AMPK and suppresses both fatty acid and cholesterol synthesis, indicating HMGR is less sensitive to AMPK activation than ACC.

3.1.3 Regulation of Acylglycerol and Cholesterol Ester Hydrolysis via Hormone-Sensitive Lipase (HSL) HSL hydrolyzes acylglycerols and cholesterol esters in animals. Although adipose tissue sensitivity to catabolic stimuli was recognized decades ago, HSL was only recently purified from rat epididymal fat pads. 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. The

opposing effects at these two sites demonstrate that AMPK phosphorylation at Ser565 prevents subsequent PKA phosphorylation at Ser563, thereby suppressing lipid breakdown. Roepstorff et al. found that post-exercise activation of AMPK$ $2 in skeletal muscle inhibits HSL activity and consequently reduces lipolysis.

3.1.4 Regulation of Triglyceride Synthesis via Glycerol-3-Phosphate Acyltransferase (GPAT) GPAT is the key enzyme for fatty acid acylation and triglyceride synthesis. Hammond et al. found that GPAT-deficient mice exhibit reduced body weight, decreased adipose tissue content, and lower hepatic TG levels, while GPAT overexpression reduces fatty acid oxidation and enhances TG esterification. Deborah et al. demonstrated that AICAR treatment of cultured rat hepatocytes for 60 minutes reduced mitochondrial GPAT activity by 29-43%, and after 90 minutes decreased incorporation of [3H]glycerol and [14C]oleate into triglycerides by 38% and 50%, respectively, while reducing [14C] incorporation into diglycerides by 60%. Saha et al. showed that low-dose AICAR feeding reduced GPAT activity in rats, suggesting AMPK-mediated regulation. Muoio et al. found that both CPT1 and GPAT localize to the mitochondrial outer membrane, and their activities may determine acyl-CoA metabolic fate. AMPK activation-induced GPAT inactivation not only suppresses fatty acid synthesis but also promotes fatty acid oxidation by reducing GPAT' s competition with CPT1 for acyl-CoA.

3.1.5 Promotion of Fatty Acid Oxidation AMPK regulates fatty acid oxidation through the AMPK-ACC-malonyl-CoA-CPT1 pathway. CPT1 transports long-chain fatty acids into mitochondria for β-oxidation. Malonyl-CoA, a physiological inhibitor of CPT1, normally maintains low fatty acid oxidation rates through allosteric inhibition under physiological conditions. During stress or AMPK activation, increased AMPK activity inhibits ACC, reducing malonyl-CoA levels and alleviating CPT1 inhibition, thereby promoting mitochondrial fatty acid β-oxidation. Studies show that AICAR treatment of human umbilical vein endothelial cells for 2 hours increases AMPK activity, decreases ACC activity, reduces malonyl-CoA concentration, and enhances palmitate oxidation. Tan et al. found that high-fat feeding reduces AMPK activity while increasing ACC activity in mice. Atkinson et al. demonstrated that ACC-β knockout mice exhibit increased food intake but reduced body fat content, indicating that ACC-β deficiency accelerates fatty acid oxidation and decreases fat accumulation.

3.2.1 Promotion of Glucose Uptake

Muscle contraction and AICAR stimulation both increase AMPK activity in rat skeletal muscle and promote glucose uptake, though through mechanisms distinct from insulin. Insulin primarily activates phosphatidylinositol-3-kinase (PI3K) to stimulate glucose uptake, and PI3K inhibitors can block this effect, with insulin resistance disrupting glucose absorption. Winder et al. found

that AICAR increases glucose uptake in rat cardiomyocytes through a PI3K-independent pathway that can be inhibited by AMPK inhibitors. Research shows that AICAR promotes translocation of glucose transporter 4 (GLUT4) from the cytoplasm to the plasma membrane, confirming AMPK' s role in GLUT4-mediated glucose uptake.

3.2.2 Inhibition of Glycogen Synthesis

AMPK' s role in glycogen metabolism regulation has been extensively studied. AMPK phosphorylates glycogen synthase (GS) at Ser7 to inhibit its activity. Young et al. further demonstrated AMPK' s role in glycogen metabolism, showing that AICAR-mediated AMPK activation in rat muscle cells increases glycogen phosphorylase (GP) activity. Vincent et al. found that treating cultured rat hepatocytes with 100 mol/L AICAR reduced glucose production by 50%, while 500 mol/L AICAR completely inhibited glucose synthesis, indicating AMPK suppresses glucose production. Wang et al. demonstrated that dietary AMPK inhibitors suppress glycogen synthase activity and significantly reduce hepatic glycogen content.

AMPK is an adenosine monophosphate-activated protein kinase that serves as a central component of protein kinase cascades and a cellular 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, alleviating insulin resistance and diabetes. Current research demonstrates that AMPK mediates metabolic regulation in major glucose and lipid metabolic tissues. Although findings from experimental animals or human medicine may not be directly applicable to livestock, AMPK research provides new insights for addressing issues in animal production. As AMPK research advances, elucidating its role in nutritional metabolic diseases will be critically important.

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