AMP-Activated Protein Kinase Regulation and Biological Actions in the Heart

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Abstract: AMP-activated protein kinase (AMPK) is a stress-activated kinase that functions as a cellular fuel gauge and master metabolic regulator. Recent investigation has elucidated novel molecular mechanisms of AMPK regulation and important biological actions of the AMPK pathway that are highly relevant to cardiovascular disease. Activation of the intrinsic AMPK pathway plays an important role in the myocardial response to ischemia, pressure overload, and heart failure. Pharmacological activation of AMPK shows promise as a therapeutic strategy in the treatment of heart disease. The purpose of this review is to assess how recent discoveries have extended and in some cases challenged existing paradigms, providing new insights into the regulation of AMPK, its diverse biological actions, and therapeutic potential in the heart. (Circ Res. 2012;111: 800-814.)

Key Words: cardiac metabolism • cardioprotection • heart failure • myocardial ischemia • protein kinases

AMP-activated protein kinase (AMPK) has gained attention over the past decade as a “cellular fuel gauge” and “super metabolic regulator.” The AMPK pathway orchestrates the cellular response to a variety of stresses in the heart, regulating metabolism, organelle function, and cell growth. The discovery of AMPK stemmed from early biochemical studies showing that acetyl-CoA carboxylase (ACC) and HMG-CoA reductase activities were regulated by phosphorylation in the liver. ACC synthesizes malonyl-CoA which is an important regulator of fatty acid synthesis, whereas HMG-CoA reductase is a key enzyme in cholesterol biosynthesis. ACC phosphorylation was found to be modulated by the concentration of adenine nucleotides. The discovery that the protein kinases for ACC and HMG-CoA reductase copurified and were regulated by AMP led to the first recognition of AMPK as a distinct entity. These early observations set the stage for the cloning and molecular characterization of AMPK and then the initial pioneering studies of AMPK in the heart.

Recent investigation has elucidated novel biological actions of AMPK that are highly relevant to cardiovascular disease. With the advent of new pharmacological approaches to activate AMPK in a specific manner, the possibility of targeting this pathway for the treatment of human disease is emerging. The purpose of this review is to assess how recent investigation has extended and in some cases challenged existing paradigms, providing new insights into the regulation of AMPK, its biological actions, and therapeutic potential in the heart.

Molecular Structure and Physiology of AMPK

The molecular structure and mechanisms regulating AMPK activation are important to understanding its physiological function and to the development of innovative strategies to activate the kinase. AMPK is a heterotrimeric complex consisting of a catalytic alpha (α) subunit and regulatory beta (β) and gamma (γ) subunits (Figure 1). The α-subunit contains the AMPK serine-threonine kinase domain, which has a critical activating residue within the catalytic cleft (Thr172). Phosphorylation of this amino acid by upstream kinases is essential for AMPK activity, and its phosphorylation status often is used as an indicator of the activation state of the kinase. The α-subunit also includes an autoinhibitory domain (residues 313–335) and AMP binding to the γ-subunit induces a conformational change that relieves autoinhibition of the complex. The “α hook” region (residues 360–394) interacts with the γ-subunit when AMP is bound, leading to a change in the configuration of the complex, which promotes activation of the catalytic domain.

The β-subunits were initially thought to function as a bridge between the α-catalytic and the γ-regulatory subunits. However, β-subunits also contain a functional glycogen-binding domain, and glycogen appears to regulate the activity of the kinase. The glycogen-binding domain binds best to glycogen with a single glucose α1–6 branch, which inhibits AMPK activation by upstream kinases.

The γ-subunits contain four potential nucleotide-binding sites termed cystathionine β-synthetase (CBS) 1–4, attributable to their structural homology to binding domains in
CBS. They also are referred to as sites 1 to 4. Recent crystallographic studies show that only sites 1, 3, and 4 bind nucleotides in the mammalian enzyme. Site 1 is a high-affinity site, which mediates the allosteric activation of the complex and binds only AMP and ATP. Site 3 is a lower affinity site that binds AMP, ADP, and ATP and influences the phosphorylation state of Thr\(^{172}\) by upstream kinases and phosphatases. Site 4 binds AMP tightly in a nonexchangeable manner.\(^{17}\)

**Molecular Mechanisms of AMPK Activation**

The activity of AMPK is primarily determined by the cellular energy state, which is reflected in the ratio of AMP (and ADP) to ATP. Cellular stress leads to the breakdown of ATP to ADP, and the subsequent production of AMP through the action of adenylate kinase (2 ADP→AMP+ATP). To a lesser extent, AMP also is generated by the cleavage of pyrophosphate from ATP and via de novo purine biosynthesis. AMP content also is determined by its degradation by AMP-deaminase and 5'-nucleotidase, and inhibition of 5'-nucleotidase is emerging as a novel strategy to activate AMPK.\(^{18}\)

Cellular AMP is highly protein-bound and the concentration of free AMP in the heart is normally in the micromolar range.\(^{19}\) ATP is present in much higher concentrations than AMP, but the predominant form of cellular ATP, Mg\(^{2+}\)ATP, has a lower binding affinity for AMPK than AMP or ADP, enabling the latter nucleotides to competitively bind to the complex.\(^{17}\)

According to the conventional paradigm, AMP is the primary activator of AMPK, but recent studies have challenged this concept. ADP is present in higher concentrations than AMP and under mild stress conditions appears to be a more important regulator of site 3, which induces a conformational change that promotes phosphorylation of the Thr\(^{172}\) site.\(^{11}\) Under more intensive stress, AMP levels increase and more important regulator of site 3, which induces a conformational change that promotes phosphorylation of the Thr\(^{172}\) residue. The catalytic cleft of activated AMPK is in a closed conformation, which protects phosphorylated Thr\(^{172}\) from being dephosphorylated by protein phosphatases (PPase). The beta-subunit also contains a glycogen binding domain (GBD) that modulates kinase activation.\(^{17}\)

**AMPK Phosphorylation and Other Posttranslational Modifications**

Phosphorylation of the Thr\(^{172}\) site markedly increases the activity of AMPK and is determined by the balance of action of upstream kinases and protein phosphatases. In the heart, the liver kinase B1 (LKB1) is the major upstream AMPK kinase. Each of the AMPK subunits contains two or more isoforms, and phosphorylation of the complexes containing the predominant \(\alpha2\) isoform is entirely dependent on LKB1 during ischemia.\(^{20}\) In contrast, the kinase responsible for phosphorylating \(\alpha1\)-containing AMPK complexes in the heart has yet to be identified.\(^{20}\)

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**Non-standard Abbreviations and Acronyms**

- ACC: acetyl-CoA carboxylase
- AICAR: 5-aminoimidazole-4-carboxamide-1-beta-D-ribofuranoside
- AMPK: AMP-activated protein kinase
- Atg1: autophagy-related 1
- cidea: cell death-inducing DFF45-like effector A
- CBS: cystathionine beta-synthetase
- eEF1: eukaryotic elongation factor-2
- FOX: fororkhead box
- GLUT: glucose transporter
- GAP: GTPase-activating proteins
- IL-6: interleukin-6
- LKB1: liver kinase B1
- MIF: macrophage migration inhibitory factor
- mTOR: mammalian target of rapamycin
- mTORC1: mTOR complex 1
- MEF: myocyte enhancer factor
- PGC: peroxisome proliferator activated receptor gamma co-activator
- PFK: phosphofructokinase
- TAK-1: transforming growth factor-activated protein kinase-1
- TSC: tuberous sclerosis complex
- ULK: Unc-51-like kinase
- WPW: Wolf-Parkinson-White

**Figure 1. Molecular structure of the AMP-activated protein kinase (AMPK) complex.** The AMPK complex is composed of a catalytic subunit (\(\alpha\), dark blue) and two regulatory subunits (\(\beta\), green and \(\gamma\), red). The \(\alpha\)-subunit contains a serine-threonine kinase domain (KD), which is highly activated by phosphorylation of the Thr\(^{172}\) residue in the catalytic cleft by upstream kinases (liver kinase B1 [LKB1], calcium-calmodulin–activated protein kinase kinase-\(\beta\) [CAMKK\(\beta\)]. AMPK is maintained in an unphosphorylated inactive state by the interaction of kinase domain with an autoinhibitory domain and with the myristoylated N-terminus of the regulatory \(\gamma\) subunit. AMP and ADP interact with the nucleotide binding sites in the \(\gamma\)-subunit induces a conformational change in the heterotrimeric complex via the \(\alpha\) hook domain (H), which relieves the autoinhibition by the autoinhibitory domain (AID) and promotes phosphorylation of the Thr\(^{172}\) residue. The catalytic cleft of activated AMPK is in a closed conformation, which protects phosphorylated Thr\(^{172}\) from being dephosphorylated by protein phosphatases (PPase). The beta-subunit also contains a glycogen binding domain (GBD) that modulates kinase activation.
The calcium-calmodulin–activated protein kinase kinase-β is a potential alternative upstream kinase that has an important role in activating AMPK in the brain and other noncardiac cells. However, calcium-calmodulin–activated protein kinase kinase-β is expressed in much lower amounts in cardiomyocytes, and its role in the heart is still not well-understood. Transforming growth factor-β–activated protein kinase-1 (TAK-1) is known to phosphorylate SNF1, the yeast homolog of the mammalian AMPK α-subunit. Although TAK-1 is present in the heart and is activated during ischemia, it appears to modulate LKB1 activity rather than directly phosphorylate AMPK.

Protein phosphatases also have a critical role in regulating Thr172 phosphorylation. Both protein phosphatase 2A and protein phosphatase 2C dephosphorylate AMPK in cell-free in vitro assays. AMP binding to the γ-subunit inhibits the action of protein phosphatase 2C to dephosphorylate Thr172 in vitro. Alterations in protein phosphatase expression modulate AMPK activation in the heart, for example, increased protein phosphatase 2C expression decreases AMPK activity in the rodent cardiac lipotoxicity model. Protein phosphatase 2A also dephosphorylates AMPK, and elevated serum fatty acids stimulate protein phosphatase 2A activity and decrease AMPK phosphorylation in endothelial cells. However, at the current time, there is limited understanding of the specific phosphatases, let alone which of their isoforms are physiologically responsible for dephosphorylating Thr172 and maintaining the low basal activity of AMPK in the normal heart.

AMPK activation also is modulated by phosphorylation at other sites. The α1-subunits are phosphorylated on Ser173, Ser485, and Ser497, whereas the β1-subunits are phosphorylated on Ser24. Phosphorylation of Ser173 by protein kinase A blunts the phosphorylation of Thr172 by upstream AMPK kinases. Ser485 in α1 and the corresponding Ser491 in α2-subunits are phosphorylated by both Akt and protein kinase A, inhibiting activation at the Thr172 site. Phosphorylation of Ser485 or Ser491 is responsible for the effect of high insulin concentrations or constitutively active Akt to blunt AMPK activation in the heart.

In addition to phosphorylation, recent evidence indicates that AMPK undergoes posttranslational acetylation of its α-subunits. The acetylation state of AMPK is determined by the reciprocal actions of the acetylase p300 and the histone deacetylase 1. Deacetylation of AMPK promotes its interaction with upstream LKB1, which phosphorylates AMPK and stimulates its activation. Interestingly, LKB1 itself is also regulated by acetylation, and the deacetylated form of LKB1 more readily leaves the nucleus and binds to its partner STRAD in the cytoplasm, forming the active LKB1 complex. These findings indicate that acetylation is a potentially important determinant of the activity of the LKB1–AMPK pathway, although there is no information on the extent to which this mechanism is operative in the heart.

**AMPK Subcellular Localization**

Subcellular localization is an important determinant of cell signaling events and targeting of protein kinases to subcellular domains provides selectivity to specific substrates. Although AMPK traditionally has been considered to be a cytosolic enzyme, evidence is emerging that it also may be targeted to the nucleus and specific membrane domains.

AMPK has well-established functions in the nucleus, where it phosphorylates transcription factors, histone proteins, and histone deacetylase enzymes. The α2, but not the α1, isoform of the AMPK catalytic subunit has a nuclear localization signal, although both α isoforms contain a nuclear export sequence. Nuclear translocation of AMPK requires phosphorylation at the Thr172 site, indicating that only activated AMPK goes to the nucleus. Exercise causes AMPK activation and nuclear translocation of AMPK complexes containing α2-subunits in skeletal muscle, but there are no published data yet demonstrating cardiac AMPK translocation to the nucleus.

Localization of AMPK to specific membrane domains is potentially another important determinant of its action. Myristoylation of AMPK at the Gly1 site of its β-subunits serves to localize the AMPK complex to membranes. Interestingly, myristoylation also increases the ability of AMP to allosterically activate AMPK and to promote phosphorylation of the Thr172 site by upstream kinases, suggesting possible preferential activation of AMPK at membrane sites. Additional mechanisms indirectly may localize AMPK to membrane domains. For instance, AMPK binds to LKB1, which localizes with E-cadherin in adherens junctions in polarized epithelial cells. The targeting of AMPK to specific membrane domains is difficult to study in cardiomyocytes but could be an important determinant of its biological activity to regulate ion channels, membrane-associated signaling proteins, cell polarity, and cell junction formation in the heart.

AMPK signaling may also be localized to specific cytosolic domains through interacting with scaffold proteins. Scaffold proteins insulate kinase pathways from surrounding signaling cascades or alternatively promote the interaction of various signaling pathways. Interestingly, AMPK interacts with the TAK-1–binding protein-1, a scaffold protein better known for its role in mediating TAK-1 activation and p38 mitogen activated protein kinase autophosphorylation. The interaction with TAK-1–binding protein-1 appears to be functionally important in the heart, where impaired AMPK activity decreases p38 mitogen activated protein kinase recruitment to TAK-1–binding protein-1 and blunts p38 activation during ischemia.

**AMPK Expression and Turnover**

Although previous attention has focused primarily on the molecular mechanisms responsible for the acute activation of AMPK complexes, the expression and turnover of AMPK, upstream LKB1, and their component subunits also are regulated. In the heart, AMPK activity increases soon after birth, contributing to the metabolic switch from carbohydrate to fatty acid metabolism. The total expression of AMPK does not appear to change significantly at birth in the mouse, but there is a developmental shift in the expression pattern of specific AMPK subunit isoforms in the heart. There are three genes (PRKAG1, PRKAG2, and PRKAG3) encoding the γ-subunit isoforms (γ1, γ2, and γ3). Transcript levels of the γ1 isoform increase whereas γ3 content decreases during the development of the embryonic mouse.
heart.42 The physiological significance of these expression patterns is uncertain and previous studies have demonstrated that AMPK activity in the adult heart is primarily determined by complexes containing the ubiquitously expressed γ1 isoform.43

The γ2 subunit expression pattern is particularly important in the heart because mutations in the human PRKAG2 gene cause a cardiomyopathy, as subsequently discussed. The PRKAG2 gene encoding the γ2 isofrom has four alternative transcripts: γ2a (long form), γ2b (short form), γ2c, and a recently discovered γ2–3B (the product of a variant transcript that starts in exon 3B).42 Of the γ2 isoforms, γ2–3B and γ2b (short form) predominate in both human and mouse hearts, and their expression increases during development.42 Interestingly, the expression of γ2–3B is relatively restricted to heart; however, it is not known whether it has distinctive physiological functions.

AMPK expression also is altered during pressure overload and after the development of heart failure. Aortic banding leads to upregulation of α2, β2, and γ2 isoforms in the rodent heart.41,44 In contrast, hearts explanted from patients with ischemic or nonischemic cardiomyopathy demonstrate increased expression of the α1, β1, and γ2c isoforms.41 These differential isoform responses are of interest, although their functional significance is not understood; whether they represent species differences or distinct responses to various types of heart failure is also unknown.

The molecular mechanisms regulating AMPK subunit expression have not been defined. However, recent studies suggest that microRNAs may play a role in regulating the upstream LKB1 complex and thus would modulate AMPK activation. Specifically, miR-451 regulates the expression of the LKB1 binding partner MO25α, a protein that is required for LKB1 activity, in glioma cells.45 Further study is needed to determine the extent to which the expression of AMPK or LKB1 in the heart is regulated by microRNAs or transcriptional regulators.

Protein degradation also is emerging as an important determinant of AMPK subunit levels. Free AMPK subunits are relatively labile when not incorporated into the heterotrimeric AMPK complex. For instance, when inactivated or "kinase-dead" α-catalytic subunits are expressed in the hearts of transgenic mice, they compete with native α-subunits for incorporation into the AMPK heterotrimeric complex and the remaining free α-subunits are degraded.46 Recent studies show that AMPK subunits are degraded by ubiquitin-dependent proteasome activity, based on findings that cell death-inducing DFF45-like effector A (cidea) knockout mice have high levels of α-, β-, and γ-subunits in adipose tissue.47 Whether a ubiquitin-dependent proteasome mechanism of AMPK degradation is operative in the heart is not yet known.

**Stimuli Activating AMPK**

Heart AMPK activity is increased by a wide array of stimuli, including pathological and physiological stress, hormones and cytokines, and drugs (Figure 2). One of the best-studied pathological stimuli for AMPK activation in the heart is ischemia.48 AMPK is activated by both severe no-flow ischemia48 and partial ischemia46 in isolated perfused rodent hearts, as well as during the regional ischemia that accompanies coronary ligation in vivo.59,60 AMPK activation is rapid and generally sustained during ischemia.51

Oxidative stress also induces AMPK activation. Hydrogen peroxide activates AMPK in isolated cardiomyocytes,52 although the mechanisms involved remain uncertain. In endothelial cells, oxidative stress triggers peroxynitrite formation,53 which is reported to increase AMPK activation through a protein kinase C zeta/LKB1-dependent mechanism.54 In nonexcitable cells, an additional mechanism mediating AMPK activation by oxidative stress involves the activation of calcium-release–activated calcium channels with subsequent calcium-induced activation of calcium-calmodulin–activated protein kinase kinase-β and downstream AMPK.55 In contrast, there also is evidence that oxidative stress might sometimes inactivate the AMPK pathway in the intact heart. In the spontaneously hypertensive rat model, LKB1 is inactivated via formation of lipid peroxidation 4-hydroxy-2-nonenal conjugates, leading to decreased activation of AMPK.56 Thus, oxidative stress might have variable effects on the AMPK pathway, depending on the degree and duration of stress and the specific stimulus inducing oxidative stress.

Pressure overload stress increases AMPK subunit expression, and also the activation state of both α1- and α2-complexes in the heart.44,57,58 The metabolic consequences of AMPK activation include increased rates of cardiac glucose transport44 and glycolysis.59 Increased expression of several metabolic genes during pressure overload is also AMPK-dependent.60 However, as previously noted, not all forms of left ventricular (LV) pressure overload activate the AMPK

![Figure 2. Regulators of AMP-activated protein kinase (AMPK) activity.](Image)
pathway in vivo, and it is also noteworthy that agonists, which induce hypertrophy in neonatal cardiomyocytes, do not increase AMPK activity.

The primary physiological stress that activates AMPK is exercise, in both skeletal muscle and the heart. The activation of heart AMPK during exercise is associated with stimulation of downstream glucose transporter (GLUT) 4 translocation and ACC phosphorylation, mechanisms that promote the metabolism of glucose and fatty acids, respectively. The degree of activation of α2-containing complexes appears greater than that of α1-complexes, consistent with the reported higher sensitivity of α2-complexes to changes in AMP concentration in vitro. However, the precise mechanisms responsible for AMPK activation during exercise are not well-defined. It is interesting that increased afterload does not appear to activate AMPK in the perfused rat heart, raising the possibility that additional factors other than simply cardiac work are required for AMPK activation during exercise.

Additional diverse pathological stimuli are known to activate AMPK in noncardiac cells, including hypoglycemia, osmotic stress, heat shock, and ultraviolet irradiation (Figure 2). Whether these mechanisms are operative or important in the intact heart is less certain. Although nutrient deprivation classically activates AMPK, it is interesting that high concentrations of palmitate or oleate appear to activate AMPK in isolated perfused hearts. These findings do not conform with the notion of AMPK as a “fuel gauge” and have been construed as a feed-forward mechanism to facilitate fatty acid oxidation. One alternative explanation is that high fatty acid concentrations might induce oxidative stress, leading to AMPK activation in the heart.

**Hormones and Cytokines in the Activation of AMPK**

The traditional paradigm of AMPK as an energy stress-activated kinase has expanded to include what might be considered an outer shell of regulation by endocrine, paracrine, and autocrine mechanisms (Figure 2). A diverse array of hormones and cytokines modulate AMPK activity in noncardiac cells, including adiponectin, leptin, resistin, ghrelin, IL-6, and ciliary neurotrophic factor. The specific mechanisms mediating these effects on AMPK are largely unknown.

In the heart, adiponectin is perhaps the best-studied AMPK-activating hormone. AMPK contributes to the cardioprotective effects of adiponectin during ischemia and inhibitory effects on cardiac hypertrophy after aortic banding. The canonical AdipoR1 and R2 are expressed in the heart, but interesting recent findings indicate that the glycoprotein T-cadherin might be the critical receptor for adiponectin binding and AMPK activation in cardiomyocytes.

The antiobesity hormone leptin also modulates AMPK activity in a variety of tissues, including fatty acid oxidation in skeletal muscle while also inhibiting AMPK in the hypothalamus, which decreases food intake. Leptin also appears to demonstrate AMPK-dependent actions in the heart. Cardiac-specific leptin receptor knockout mice have impaired activation of AMPK after myocardial infarction, which is associated with impaired glycolytic metabolism, increased apoptosis, and adverse LV remodeling. In addition, ischemic postconditioning and AMPK activation are impaired in hearts of leptin-deficient ob/ob mice subjected to ischemia/reperfusion, indicating a modulating effect of leptin on AMPK activation in the heart.

Proinflammatory cytokines also modulate AMPK activation. In the heart, short-term IL-6 infusions appear to reduce AMPK α-subunit content and activation. Mice fed a high-fat diet have elevated plasma levels of IL-6, which may contribute to the downregulation of AMPK seen in this model. In contrast, IL-6 has a specific autocrine–paracrine effect in skeletal muscle to augment AMPK activation, whereas intravenous infusion of IL-6 has little effect on muscle AMPK activity.

Macrophage migration inhibitory factor (MIF) is a master-regulator of inflammatory cytokines but also, curiously, is highly expressed in cardiomyocytes. Hypoxia increases cardiac MIF expression via a hypoxia-inducible factor-1–dependent mechanism, and ischemia triggers MIF secretion. Endogenous cardiac MIF has an important autocrine–paracrine action to modulate AMPK activation during ischemia and hypoxia in the heart. Extracellular MIF activates AMPK via its cell surface receptor CD74 with subsequent activation of the signal transducer CD44. Knockout mice have impaired heart AMPK activation and are more susceptible to ischemic injury. These observations have potential clinical relevance based on the observation that a common polymorphism in the MIF gene promoter leads to diminished MIF release and AMPK activation in response to hypoxia in human cells. In addition, heart MIF expression is decreased with aging and appears to be responsible for diminished AMPK activation during ischemia in old mice. These findings raise the possibility that older patients or those with the low-expression MIF gene promoter polymorphism may be at increased risk for ischemic injury and might be more likely to benefit from therapeutics targeting AMPK activation.

**Pharmacological AMPK Activators**

A number of pharmacological compounds have been identified that activate AMPK (Figure 2). The first one recognized was the nucleoside 5-aminimidazole-4-carboxamide-1-beta-D-ribofuranoside (AICAR), which is taken-up by cells and phosphorylated to the AMP-mimetic “ZMP.” AICAR increases AMPK activity in several tissues, including the heart. However, AICAR also is an adenosine-regulating agent that was developed as “Acadesine” to protect the heart during cardiac surgery, although it is unclear whether the doses administered were adequate to activate AMPK in the human heart. AICAR is used extensively for experimental studies, but its complex pharmacology leads to variable degrees of AMPK activation and its off-target effects render it less than ideal as a drug for mechanistic studies.

The diabetes drug metformin activates AMPK in various cell types, including cardiomyocytes. Metformin inhibits complex 1 of the mitochondrial electron transport chain, which leads to an increase in the AMP to ATP ratio. Recent data suggest that metformin might have an additional effect to inhibit AMP deaminase activity, which would increase intracellular AMP concentrations and activate AMPK.
rectly. Metformin also activates heart AMPK when administered to mice, and has a potent cardioprotective action in the post-ischemic mouse heart. However, metformin also has important AMPK-independent effects, such as its well-known action of suppressing hepatic glucose production in type 2 diabetes. A second important class of diabetes drugs, the thiazolidinediones, also activate AMPK in the heart. However, it is not clear that they activate AMPK in the human heart at clinically prescribed doses and caution is warranted in terms of attributing their clinical cardiovascular effects to AMPK activation.

The lack of specificity of existing drugs has spurred an interest in the development of more direct and specific AMPK activators. Initial screens yielded compounds that interact directly to activate the AMPK complex. The thienopyridone compound A769662 interacts with β1-subunits and activates AMPK through allosteric mechanisms and by increasing phosphorylation of the Thr172 site. In the heart, A769662 preconditions the heart through an AMPK-dependent mechanism. Recently, the compound PT1 was shown to activate AMPK through interaction with the α1-subunit at the Glu46 and Lys156 sites that are adjacent to the autoinhibitory domain. PT1 promotes phosphorylation of Thr172 and activates AMPK in an AMPK-independent fashion in L6 myotubes. Although both of these novel compounds have relatively low potency, they serve as prototypes for the development of additional agents.

Two commonly used nondiabetes drugs also have been reported to activate AMPK. Statins activate AMPK in endothelial cells and AMPK appears to mediate their effect to promote nitric oxide production and angiogenesis. The administration of atorvastatin to mice stimulates AMPK activation in the aorta and in the myocardium, although at doses that exceed those prescribed clinically. A recent intriguing study demonstrates that salicylate also activates AMPK in noncardiac cells through binding to the same β-subunit site that interacts with A769662. The salicylate concentration required to activate AMPK is in the upper range of levels observed with high-dose aspirin treatment. Although potentially relevant to high-dose aspirin therapy in patients with inflammatory disease, these results likely have limited relevance to the traditionally low doses of aspirin prescribed to patients with cardiovascular disease.

AMPK activation by drugs, hormones, and cytokines can involve subtle increases in the cellular ratio of AMP to ATP that are difficult to detect. AMP is present in low concentrations, and direct measures of the biologically active nonprotein-bound free AMP concentration are not feasible in intact cells. One innovative approach to determining whether drugs or hormones activate AMPK through alterations in the cellular AMP content is by testing them in cell lines that express AMPK complexes containing mutant isofoms that are insensitive to AMP. This approach shows AMP dependence for many compounds, but A769662 and salicylate activate AMPK in an AMP-independent fashion.

Additional strategies are undergoing investigation to activate AMPK by decreasing AMP degradation. Knockdown of the AMP-degrading enzyme 5′-nucleotidase increases the ratio of AMP to ATP, enhancing AMPK phosphorylation and the downstream activation of ACC and glucose transport in both myotubes and mouse skeletal muscle. Although these results are of interest, the efficacy of inhibiting 5′-nucleotidase in the heart is not yet established and the potential sequelae of altering nucleotide metabolism warrant further consideration.

### AMPK Inhibitors

Pharmacological inhibitors are useful reagents to probe the function of protein kinases in both cells and intact animals. Unfortunately, like many kinase inhibitors, the existing AMP inhibitors lack specificity. The most widely used inhibitor, compound C, inhibits AMPK in vitro with an IC50 of 0.1 to 0.2 μmol/L. However, even at a concentration of 1 μmol/L, which is lower than typically used for most cell-based experiments, compound C inhibits multiple other protein kinases, such as extracellular signal-regulated kinase 8, Src kinase, and mitogen activated protein kinase kinase-interacting serine/threonine-protein kinase 1. This lack of specificity makes it highly desirable to use complementary genetic approaches to inactivate the AMPK pathway rather than to rely primarily on pharmacological results.

### Metabolic Pathway Regulation by AMPK

AMPK activation coordinates the regulation of several steps in substrate transport and metabolism, which are critical for energy generation and conservation under times of stress (Figure 3). The metabolic actions of AMPK were instrumental in focusing scientific interest in understanding the AMPK pathway in the heart. The earliest work on AMPK focused on its role in modulating cardiac fatty acid oxidation. The phosphorylation of ACC2 inhibits its activity and the synthesis of malonyl-CoA, a potent inhibitor of carnitine palmitoyltransferase-1. The decrease in malonyl-CoA levels relieves the inhibition of carnitine palmitoyltransferase-1, which transports fatty acyl-CoA groups into the mitochondrial matrix and is the rate-limiting step for heart fatty acid oxidation.

AMPK is rapidly activated by ischemia, but it has no discernible effect to increase fatty acid oxidation during ischemia because of the absence of oxygen. However, AMPK activation persists for variable periods of time during reperfusion and plays a role in reactivating fatty acid oxidation early in the postischemic heart. AMPK also stimulates the myocardial uptake of fatty acids by increasing the translocation of the fatty acid transporter CD36 from intracellular storage membranes to the sarcolemma. In addition, AMPK activates lipoprotein lipase, which facilitates cardiac fatty acid uptake from triglyceride-containing lipoprotein particles. Thus, activated AMPK has several effects that act in concert to promote fatty acid oxidation.

AMPK also stimulates glucose transport and glycolysis, which are particularly important to the metabolic adaptation of the ischemic heart. Glucose uptake is mediated by GLUT4 and, to a lesser extent, by GLUT1 in the heart, and AMPK has an important effect to stimulate GLUT4 translocation to the sarcolemma. Neither GLUT4 nor GLUT4-containing vesicles are directly phosphorylated by AMPK. Rather, AMPK phosphorylates Rab GTPase-activating proteins that...
regulate Rab10, which modulates docking and fusion of GLUT4 vesicles with the plasma membrane. The Akt substrate 160 protein is a GTPase-activating proteins expressed in heart and it regulates the GTP form of Rab10. In addition, AMPK also may inhibit endocytosis of GLUT4 in cardiomyocytes, increasing the sarcolemma GLUT4 content and glucose transport. AMPK also acts downstream to glucose transport by indirectly increasing the activity of phosphofructokinase-1, the rate-limiting enzyme in glycolysis. Activated AMPK directly phosphorylates and stimulates phosphofructokinase-2 to synthesize fructose 2,6-bisphosphate, which in turn allosterically activates phosphofructokinase-1. These increases in myocardial glucose transport and glycolysis are important components of the metabolic response to ischemia or hypoxia. 

**AMPK Regulation of Transcription**

In addition to the well-established acute metabolic effects of AMPK, AMPK also translocates into the nucleus, where it has more prolonged effects on cellular metabolism by regulating gene transcription. In the heart, AMPK regulates genes related to mitochondrial energy metabolism, including medium chain acyl-CoA dehydrogenase, carnitine palmitoyltransferase-1, cytochrome C, and uncoupling protein-3. These effects are mediated in part by activation of the estrogen-related receptor-α transcription factor.

AMPK also appears to regulate peroxisome proliferator-activated receptor-γ coactivator (PGC)-1α, a critical modulator of cardiac gene expression and mitochondrial biogenesis. AMPK activation increases the expression of PGC-1α in hypoxic cardiomyocytes. More detailed mechanisms linking AMPK to PGC-1α and mitochondrial biogenesis have been delineated in skeletal muscle. AMPK increases muscle NAD⁺ concentrations and the activity of the NAD⁺-dependent deacetylase sirtuin-1 during fasting and exercise, and the subsequent deacetylation of PGC-1α promotes its activity. How AMPK increases cellular NAD⁺ concentration is less certain but may result in part from increased expression of the NAD⁺ biosynthetic enzyme nicotinamide phosphoribosyltransferase. AMPK also directly phosphorylates and activates PGC-1α at Thr177 and Ser538. In addition, chronic activation of AMPK also enhances the binding activity of nuclear regulatory factor-1 and mitochondrial biogenesis in skeletal muscle. The extent to which these mechanisms function in the heart is unclear, but they could be important to the regulation of mitochondrial biogenesis during growth and cardiac hypertrophy.

AMPK also modulates gene expression through novel mechanisms in noncardiac cells. AMPK phosphorylates the histone deacetylase 5 transcriptional repressor at both the Ser259 and Ser498 sites, which promotes GLUT4 transcription in myotubes. Activated AMPK acts as a direct histone kinase, phosphorylating histone 2B on Ser14 and regulating gene transcription. AMPK also modulates the stability of mRNA transcripts by regulating the egress of the RNA-binding protein HuR to the cytoplasm. Further studies will be needed to determine whether these mechanisms are operative in cardiomyocytes.

**AMPK Regulation of Protein Synthesis**

AMPK has important actions to inhibit cellular protein synthesis, in line with its role to conserve energy by inhibiting energy-consuming biosynthetic pathways (Figure 4). Under conditions of potentially lethal energy deprivation, there is little need to consume ATP to synthesize long half-life proteins. Among the best-characterized targets of AMPK is the eukaryotic elongation factor-2 kinase, which AMPK phosphorylates at Ser209, leading to the phosphorylation and inhibition of downstream eukaryotic elongation factor-2. This action may be functionally important in the heart to conserve energy during ischemia and to prevent excess hypertrophy during pressure overload.

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**Figure 3. AMP-activated protein kinase (AMPK) regulation of heart glucose and fatty acid metabolism.** AMPK regulates substrate transporters and the concentrations of allosteric regulators of glycolysis and fatty acid oxidation. AMPK phosphorylates the Rab GTPase AS160, which induces glucose transporter (GLUT) 4 translocation to the sarcolemma. AMPK phosphorylates phospho-fructokinase 2 (PFK2), leading to the synthesis of fructose-2,6-bisphosphate, an allosteric activator of PFK1 and glycolysis. AMPK promotes lipoprotein lipase (LPL) translocation from the myocyte sarcolemma to the luminal surface of capillary endothelial cells, where it catalyzes the release of long-chain fatty acids (LCFA) from triglyceride-containing lipoproteins for heart substrate metabolism. Activated AMPK also stimulates CD36 translocation to the sarcolemma, increasing cardiomyocyte free fatty acid uptake. AMPK also phosphorylates and inactivates acetyl-coenzyme A carboxylase (ACC), decreasing the concentration of the fatty acid oxidation inhibitor malonyl-CoA. Molecules that are phosphorylated by AMPK are designated by the symbol “P”. Proteins directly activated by AMPK are highlighted in red and proteins inactivated by AMPK are in gray. Illustration credit: Ben Smith.
AMPK Regulation of Protein Degradation and Autophagy

AMPK also modulates protein degradation and the turnover of intracellular organelles. AMPK activates the ubiquitin proteasome system and protein degradation in striated muscle cells and in the heart. In the heart, AMPK increases the expression of the ubiquitin ligases atrogin-1 and the muscle RING finger protein 1, the latter through activating MEF2. Whether muscle RING finger protein 1 upregulation requires PGC-1α activation and how AMPK activates MEF2 in cardiomyocytes is uncertain. It would also appear that there is a complex interplay between AMPK and MEF2, and that activated AMPK counters the effect of MEF2 to promote cardiac hypertrophy.

In keeping with its function to provide energy during nutritional deprivation, AMPK also promotes autophagy, providing important nutrients from the breakdown of macromolecules and organelles. In the ischemic heart, AMPK activation induces autophagy in cardiomyocytes, contributing to their survival. In a diabetic mouse heart failure model, autophagy is impaired and metformin treatment enhances autophagic activity, leading to the preservation of cardiac function through an AMPK-dependent mechanism.

The molecular mechanisms responsible for the stimulation of autophagy by AMPK are now starting to be unraveled in noncardiac cells (Figure 4). AMPK inactivates mTORC1, which normally suppresses autophagy when the nutrient supply is adequate. Intriguing recent evidence also indicates that AMPK directly phosphorylates the Unc-51-like kinase (ULK) 1, the mammalian homolog of the yeast kinase autophagy-related 1 (Atg-1), which has a critical role in the induction of autophagy. AMPK is reported to phosphorylate ULK-1 on various sites, including Ser467, Ser555, Thr574, Ser637, Ser637, and Ser757. Interestingly, loss of function of either AMPK or ULK-1 results in defective mitophagy. AMPK appears to bind in a complex that includes ULK-1 and mAtg101, and this interaction is nutritionally dependent and is inhibited by mTOR phosphorylation of ULK-1 on Ser757. Thus, there is a complicated interplay between AMPK, mTORC1, and ULK-1 in regulating autophagy and the specific molecular mechanisms through which AMPK regulates autophagy during ischemia, hypertrophy, and heart failure require additional investigation.

AMPK Action During Myocardial Ischemia-Reperfusion

AMPK is activated during ischemia, and most evidence indicates that intrinsic AMPK activation protects the heart against injury during ischemia-reperfusion. Genetic inhibition of heart AMPK by the transgenic expression of an inactive K45R α2 subunit impairs ischemic glucose uptake and ATP homeostasis and results in poor recovery of LV contractile function, increased cardiac necrosis, and greater apoptosis after ischemia-reperfusion. Similarly, hearts from mice expressing the inactive D157A α2 subunit have reduced glucose uptake and greater ATP depletion during ischemia and increased necrosis after coronary occlusion-reperfusion in vivo. Hearts from global AMPK α2 knockout mice have reduced glycolysis, greater ATP depletion, more rapid development of contracture during ischemia, as well as impaired metabolism and contractile function after ischemia. However, not all studies have documented a protective function of the AMPK pathway during ischemia.

AMPK inactivation models provide insight into the intrinsic role of the AMPK pathway in the response to ischemia. However, from the clinical perspective, the more important issue is whether pharmacological AMPK activation represents a potential therapeutic strategy to reduce ischemic injury, and evidence to date supports this possibility. Metformin activates AMPK and protects against regional ischemia when administered in vivo in both diabetic and normal mice, before or after ischemia. The compound A769662, which directly activates AMPK, protects against ischemic injury during global ischemia in vitro and during regional ischemia in vivo. A769662 treatment also enhances ischemic AMPK activation and reduces...
AMPK Action in Cardiac Hypertrophy

Cardiac hypertrophy has an adaptive function to reduce wall tension in the setting of the LV pressure overload that accompanies hypertension or obstructive valvular heart disease. However, pressure overload can lead to pathological LV remodeling, characterized by hypertrophy exceeding vascular perfusion capacity, interstitial fibrosis, diastolic dysfunction, or overt systolic contractile failure. Thus, strategies that limit LV remodeling are potentially important and AMPK activation appears to modulate the myocardial response to pressure overload.

The effects of prohypertrophic stimuli are blunted by treatment with pharmacological agents that activate AMPK. For instance, metformin, AICAR, and resveratrol each activate AMPK and diminish hypertrophy induced by either phenylephrine or constitutively active Akt in neonatal rat cardiomyocytes. Adiponectin also decreases agonist-induced cardiomyocyte hypertrophy in vitro in an AMPK-dependent fashion, as does constitutively active AMPK. In contrast, the diabetic heart has increased expression of the hormone resistin, which inhibits AMPK activation, worsening hypertrophy in neonatal rat cardiomyocytes. Taken together with the known effects of activated AMPK to inhibit protein synthesis, these data support the paradigm of AMPK functioning as an antihypertrophic pathway in the cardiomyocyte.

In the intact heart, intrinsic activation of AMPK appears to have an important role in the functional response to pressure overload. Mice with global α2 AMPK deletion demonstrate greater hypertrophy, contractile dysfunction, fibrosis, heart failure, and mortality after aortic banding. Greater activation of the mTOR/S6-kinase signaling pathway, which is normally inhibited by AMPK, likely contributes to the excess hypertrophy in this model. Exaggerated cardiac hypertrophy and contractile failure also occur in adiponectin knockout mice, which have reduced AMPK phosphorylation after aortic banding. Recent data indicate that AMPK deficiency also exacerbates obesity-induced cardiac hypertrophy and contractile dysfunction.

Although AMPK restrains the development of pathological hypertrophy during aortic banding, intrinsic AMPK activation does not appear to regulate normal heart growth. It is striking that none of the mouse models with impaired heart AMPK activation develop cardiac hypertrophy. The greater influence of AMPK activation during pressure overload hypertrophy might reflect the fact that AMPK activation is more sustained after banding, as compared to the intermittent AMPK activation associated with exercise during normal growth. AMPK also blocks the hypertrophic response to aortic banding by blunting the increase in cardiac angiotensin II and endothelin concentrations and inhibiting the nuclear factor-κB and the calcineurin/nuclear factor of activated T-cell pathways.

From a translational perspective, there appears to be an opportunity for therapeutic intervention, because AMPK activity is not maximally increased during pressure overload and can be further augmented by pharmacological means. Treatment with the AMPK activator AICAR blunts LV hypertrophy induced by aortic banding in rats, although AICAR also decreased blood pressure, confounding interpretation of these results. Resveratrol has similar beneficial effects on AMPK and hypertrophy in this model but has pleiotropic effects that might contribute to its action. Adiponectin overexpression also activates AMPK in the heart and diminishes hypertrophy after banding in mice. Thus, these initial observations support the possibility that AMPK activators might have a role in modulating the hypertrophic...
AMPK in Heart Failure

Heart failure is associated with numerous alterations in cardiac substrate and energy metabolism, leading to an interest in understanding the role of AMPK in mediating these changes and the potential benefit of pharmacologically activating AMPK in failing hearts. In the rapid pacing-induced canine heart failure model, both metformin and AICAR treatment significantly diminish contractile dysfunction, apoptosis, and fibrosis. Both treatments augment AMPK activation in the paced hearts, suggesting that heart failure does not maximally activate the AMPK pathway and that further pharmacological activation might be beneficial. These treatments also improve systemic insulin resistance and increase plasma nitric oxide levels, and it is possible that these noncardiac effects might contribute to their beneficial effects. Metformin and AICAR also have additional effects on the heart, the former as a mitochondrial complex 1 inhibitor and the latter as an adenosine regulator. Some caution is warranted because the dose of metformin in experimental studies exceeds the doses used clinically. However, recent observational studies suggest that metformin improves the survival of patients with heart failure and type 2 diabetes, supporting the possibility that pharmacological activation of AMPK might be beneficial in heart failure.

AMPK also appears to play a role in preventing heart failure in the mouse coronary occlusion model. Metformin administered at the time of reperfusion augmented AMPK activation, endothelial nitric oxide synthase phosphorylation, and PGC-1α expression, and reduced LV remodeling 4 weeks after myocardial infarction. AMPK activation had a critical role in mediating the action of metformin, based on the observation that metformin had no effect in mice with genetically inactivated AMPK in the heart.

As evidence accumulates that AMPK activation might be beneficial in preventing heart failure, a number of issues require careful consideration. First, there needs to be a better understanding of whether AMPK activation has benefit in the treatment of established LV dysfunction and heart failure, recognizing that these effects might vary depending on the model. Second, the specific role of AMPK activation needs to be confirmed to be certain that observed effects are attributable to AMPK activation; more specific AMPK activators and the use of AMPK-inactivated genetic models will be important in this regard. Finally, the long-term therapeutic efficacy and safety of AMPK activators will need to be assessed.

AMPK γ-Subunit Mutations

Mutations in the gene encoding the γ2-subunit (PRKAG2) on chromosome 7q3 are linked to familial hypertrophic cardiomyopathy associated with the Wolff-Parkinson-White (WPW) syndrome. Unlike the more common forms of hypertrophic cardiomyopathy that are associated with mutations in sarcomeric proteins, the hallmark of the PRKAG2 syndrome is the accumulation of glycogen in cardiomyocytes without myofibrillar disarray. PRKAG2 mutations cause cardiac glycogen overload similar to Pompe disease or Danon disease but do not cause impaired glycogenolysis.

PRKAG2 mutations fall within or adjacent to the nucleotide binding domains (Figure 5). The degree of hypertrophy and associated conduction system disease vary depending on the mutation and the individual. The combination of hypertrophic cardiomyopathy and WPW syndrome have been linked to mutations at H383R in CBS2, T400N in CBS2, N488I in CBS3, R531G in CBS1, and R302Q in CBS4 and a leucine insertion between CBS1 and CBS2. In addition, the R531G mutation in CBS4 has been observed in children with WPW syndrome and conduction system disease without cardiac hypertrophy.

The molecular mechanisms responsible for the PRKAG2 phenotype are under investigation. Complexes containing γ2 mutations generally have diminished activation by AMP in cell-free systems, with reduced AMP dependence (R302Q, H338R) or sensitivity (N488I, R531Q, R531G) in vitro. They also appear to have reduced ATP binding, which diminishes the inhibitory effects of ATP on AMPK activation. Although mouse hearts expressing the N488I, R531G, and R302Q mutations all demonstrate cardiac glycogen overload, LV hypertrophy, and ventricular pre-excitation, they are reported to have variable AMPK activity. The N488I hearts have constitutively high AMPK activity, whereas AMPK activity in the R531G hearts is normal at 1 week and then decreases after the glycogen accumulation. Surprisingly, R302Q hearts have low AMPK activity. The reason for these disparities in AMPK activity remains uncertain.

The N488I mouse model is the best studied to date and has constitutively high AMPK activity. The N488I phenotype is largely reversed when crossed with mice expressing inactivated AMPK in the heart. The increase in activity of the N488I complex is attributable to a high level of Thr172 phosphorylation. The high AMPK activity promotes glycogen synthesis, leading to cardiac glycogen overload that is the hallmark of the PRKAG2 syndrome.

The finding that glycogen synthesis is increased in the PRKAG2 model appears paradoxical from the perspective that activated AMPK phosphorylates and inhibits glycogen synthase in noncardiac cells. However, AMPK stimulation of heart glucose uptake leads to an increase in glucose-6-phosphate concentrations, which both increase substrate availability and allosterically activate glycogen synthase. Because AMPK also increases fatty acid oxidation, which
inhibits glucose oxidation, glucose-6-phosphate is preferentially shunted into glycogen synthesis in the N488I hearts. These hearts also have increased expression of UDP-glucose pyrophosphorylase, which synthesizes UDP-glucose, the direct substrate for glycogen synthesis, although this enzyme is not rate-limiting for glycogen synthesis. Thus, increased AMPK activity and glucose uptake in the absence of increased energy demand promote glycogen accumulation in the N488I model.

The development of the WPW syndrome in patients with PRKAG2 mutations is an example of how altered metabolism affects cardiac electrophysiological development. WPW syndrome is characterized by ventricular pre-excitation via one or more muscle bridges traversing the anulus fibrosis, which “bypass” the atrioventricular node and rapidly depolarize the ventricles. These bridges normally undergo apoptosis before birth; however, in the N488I model, glycogen-filled myocytes are presumably resistant to apoptosis and persist as physiological bypass tracks that disrupt the anulus fibrosis. Consistent with the developmental basis of WPW syndrome, postnatal induction of the PRKAG2 mutation in mice fails to induce ventricular pre-excitation, although it does cause LV cardiac glycogen overload.

Because the PRKAG2 mutations appear to be activating in some cases, this research has raised concerns that AMPK activators might cause cardiac glycogen overload with prolonged use in the clinical setting. However, there are potential biological differences between the cardiac effects of AMPK activating therapy and chronically activating PRKAG2 mutations. The degree of AMPK activation might differ, and the γ mutations also might alter the subcellular distribution of AMPK or its interaction with specific substrates. It is also noteworthy that existing diabetes drugs that activate AMPK do not cause cardiac glycogen overload, although the actual degree to which they activate AMPK in the human heart is not known. Nonetheless, if excess cardiac glycogen accumulation emerges as a clinical problem, then AMPK activators would have to be restricted to use on a short-term basis, or alternative pharmacological strategies that activate AMPK outside of the heart would have to be considered.

Conclusions

In the past decade, there has been substantial progress in understanding the biological actions of AMPK and a growing appreciation of its importance in the cardiovascular system, but substantial gaps in knowledge remain to be addressed. In discussing many of the recent novel molecular mechanisms responsible for AMPK activation and action, it is readily apparent that most have been discovered in noncardiac cells. Some of these mechanisms might be ubiquitous, whereas others might not prove to be operative in the heart.

Activation of AMPK is a highly regulated process that goes beyond changes in AMP and ATP, and the role of local autocrine–paracrine factors, upstream kinases including calcium-calmodulin–activated protein kinase kinase-β, and specific protein phosphatases in the heart are all areas that require further investigation. There is also a fundamental lack of understanding of the cell biology of AMPK complexes in the heart with respect to their subcellular localization and action. Although the complex membrane structure and myofibrillar proteins pose technical challenges to studying compartmentalized signaling mechanisms, this is a key area that warrants innovative approaches to unravel. The heterogeneity of cell types in the heart presents an additional challenge to understanding the function of the AMPK pathway in the intact heart, because AMPK might be differentially regulated in endothelial cells, fibroblasts, and smooth muscle cells.

Although the acute metabolic actions of AMPK in the heart are fairly well-characterized, the regulation of gene expression in the heart by AMPK is in its infancy and further research in this area is needed. Similarly, the degree to which AMPK regulates mitochondrial function, autophagy/mitophagy, and electrophysiological properties of the heart requires additional investigation, particularly in relevant models of myocardial ischemia, pressure overload, and heart failure.

The function of specific AMPK subunit isoforms has not yet been delineated in the heart. In particular, whether the individual γ2 variants confer distinct physiological actions to AMPK complexes is an open issue. Defining the regulation and action of the γ2 variants might provide additional insight into the pathogenesis of the human PRKAG2 syndrome.

The potential translation of basic research on AMPK to the clinical arena is a goal of many ongoing research programs. Since the first discoveries that activated AMPK stimulates glucose transport in skeletal and heart muscles, there has been a great deal of interest in the development of highly potent and specific AMPK activators for the treatment of type 2 diabetes. Because diabetic patients often have concomitant cardiovascular disease, understanding the potential cardiovascular benefits and any safety issues associated with AMPK activators would be important.

With regard to the potential clinical applications of AMPK activators in cardiovascular disease, there is still much work that needs to be performed. For application to ischemia-reperfusion, additional research is clearly needed to better assess the efficacy of AMPK activators administered at the time of reperfusion. Protective effects at the time of reperfusion would enhance the use of AMPK activators as potential adjunct therapy to coronary revascularization in patients with acute myocardial infarction. If long-term therapy with AMPK activators proves feasible, then it would be appropriate to consider their application to the treatment of heart failure. Additional studies would be needed to determine whether AMPK activators prevent the transition to heart failure and, most importantly, whether they reverse LV dysfunction and adverse remodeling in the setting of established heart failure. Establishing efficacy and safety in large animal models would be essential before AMPK activators would be appropriate for introduction into clinical studies. Nonetheless, existing results to date offer encouragement to further pursue research on AMPK as a novel target for the treatment of cardiovascular disease.

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References


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108. Zaha and Young AMPK in the Heart


