AMP-Activated Protein Kinase
Potential Role in Cardiac Electrophysiology and Arrhythmias

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AMP-activated protein kinase (AMPK), a serine/threonine kinase, is a highly conserved homeostatic regulatory enzyme with a plethora of important roles in energy storage and use. ATP is the primary cellular energy source; in situations of metabolic deficiency, its breakdown product AMP accumulates. AMPK is sensitive to the cellular energy state: it is activated by AMP and inactivated by ATP. Under metabolic stress, when the AMP/ATP ratio is elevated, AMPK acts as an energy sensor and compensates for energy depletion by upregulating energy sources and downregulating energy-consuming processes that are not immediately essential.1-5 There is growing recognition that AMPK is particularly important in the heart, which demands more energy on a continuous basis than most other organs.1,2 AMPK seems to be a critical regulator of cardiac energy status and may be a potential therapeutic target. In this article, we will review the literature regarding cardiac AMPK and discuss evidence for a potentially important and underappreciated role of AMPK in cardiac electrophysiology and arrhythmia generation.

AMPK Structure
AMPK is a heterotrimeric enzyme with 1 catalytic (α) and 2 regulatory (β and γ) subunits (Figure 1). Thr-172 in the α-subunit is a crucial phosphorylation site that regulates AMPK function. The β-subunit has 2 structural components: a glycogen-binding domain that is sensitive to fuel storage levels and a C-terminal region that anchors α- and γ-subunits. The γ-subunit has a pair of cystathionine-β-synthase sequence repeats, called Bateman domains, which bind adenosine nucleotides.1-5 AMP binding to the γ-subunit facilitates Thr-172 phosphorylation by upstream kinases, protects the site against dephosphorylation by protein phosphatases (PPs), and allosterically activates the enzyme. The crystal structure of AMPK has recently been resolved, revealing how the regulatory domain stabilizes the activation loop of the kinase domain and prevents dephosphorylation.6 Various isoforms of the AMPK subunits have been identified (α1, α2, β1, β2, γ1, γ2, γ3), potentially leading to the formation of 12 different complexes.1-5 The α2, β2, and γ2 subunits predominate in the heart, which mainly expresses α2/β2/γ2 complexes.1 Activated AMPK phosphorylates a wide range of signaling systems and effectors, with major functional consequences (Figure 2).

Activation of AMPK
AMPK activation is favored by 3 nonexclusive mechanisms that often occur simultaneously: (1) allosteric activation, (2) α-subunit phosphorylation by upstream AMPK kinases (AMPKKs), and (3) inhibition of PP-mediated α-subunit dephosphorylation.1-6 AMP binding promotes AMPK activation by allosterically activating the enzyme, making it a poorer substrate for PPs and a better substrate for AMPKK.7 ADP binding also protects AMPK from dephosphorylation.6 Although the AMPK-binding affinity to ATP is high, its affinity for Mg-ATP, the predominant intracellular form, is much lower, explaining why ADP and AMP (with substantially lower physiological concentrations than ATP) can compete with ATP for binding.5 Metabolic dysfunction increases intracellular AMP concentrations, enhancing AMP binding to the cystathionine-β-synthase motif in the γ-subunit. AMPK activation occurs with a half-maximally activating AMP concentration (A0.5) of 4 μmol/L and full activation by 10 μmol/L, within the physiologically attainable range.7-8 ATP antagonizes activation via AMP by competing with AMP for binding at the allosteric site, without promoting the active conformation.3 The A0.5 increases about 20-fold when intracellular ATP concentration increases from 0.2 to 4 mmol/L.1

Phosphorylation of the α-subunit Thr-172 by upstream AMPKKs crucially regulates AMPK function. Combined AMPK activation by AMP and AMPK phosphorylation produces a 1000-fold increase in AMPK activity, whereas AMP alone elicits only a 5-fold maximum increase.3 Two major AMPKKs are present in the heart: liver kinase B1 (LKB1), also known as serine/threonine kinase 11,9 and Ca2+/calmodulin-dependent protein kinase (CaMK). LKB1 is much more abundantly expressed in the heart than CaMK.2 The amphipathic αG-helix in the AMPK α-subunit interacts with LKB1.10 LKB1 reacts to myocardial ischemia by phosphorylating the α2-subunit.1 CaMK, particularly the CaMKβ (CaMKK2) isoform, phosphorylates and activates AMPK on elevation of intracellular Ca2+ concentration.4

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The transforming growth factor-β–activated kinase, a member of the mitogen-activated protein kinase kinase family, is also implicated in AMPK activation.11

PPs, particularly PP2A and PP2C, regulate AMPK activity by dephosphorylating Thr-172. AMP binding to the γ-subunit induces a conformational change in the α-subunit that prevents AMPK dephosphorylation by PPs.3

AMPK and Cardiac Metabolism

AMPK phosphorylates a variety of enzymes that play important roles in cardiac metabolism (Figure 2), with a net effect to increase energy availability.

Fatty Acid Metabolism

Once activated under conditions of metabolic stress, AMPK enhances cellular energy availability. AMPK stimulates fatty acid oxidation (a major cardiac energy source) by phosphorylating and inhibiting acetyl-CoA carboxylase, the rate-limiting enzyme in malonyl-CoA synthesis. Malonyl-CoA inhibits carnitine palmitoyltransferase-1, a mitochondrial enzyme that facilitates fatty acid entry into the mitochondria for oxidation. Phosphorylation of acetyl-CoA carboxylase by AMPK inactivates acetyl-CoA carboxylase, thereby inhibiting malonyl-CoA production.12 The resulting decrease in malonyl-CoA concentrations disinhibits
carnitine palmitoyltransferase-1 and promotes fatty acid oxidation.1,2,4,5,12

AMPK increases the expression of the fatty acid transporter fatty acid translocase/CD36 and membrane-associated fatty acid–binding protein, both of which are involved in cellular fatty acid uptake. AMPK also recruits lipoprotein lipase, which extracts fatty acid molecules from triglycerides and enhances fatty acid availability.

Glucose Metabolism
AMPK is involved in carbohydrate metabolism, independently of insulin-mediated mechanisms. The AMPK-dependent regulation of carbohydrate metabolism is particularly important in pathological conditions, in which oxygen depletion and anaerobic glycolysis are of primary concern, whereas insulin-dependent regulation predominates at rest or during physiological stresses, such as exercise. Activated AMPK increases the protein expression of glucose transporters GLUT1 and GLUT4, increasing cellular glucose uptake. GLUT4 is also trafficked into the membrane from intracellular stores on AMPK activation.1 AMPK does not directly phosphorylate GLUT4: other AMPK targets, such as protein kinase C, p38 mitogen–activated protein kinase, and transforming growth factor-β, regulate GLUT4 function.13 Activated AMPK also phosphorylates protein kinase 1–binding protein, may mediate the enhancement of GLUT4 function.13 Activated AMPK also phosphorylates phosphofructokinase-2 to convert fructose-6-phosphate to fructose-2,6-bisphosphate.1–5 Fructose-2,6-bisphosphate acts as a allosteric activator of phosphofructokinase-1, which accelerates glycolysis. Therefore, AMPK activation promotes both glucose uptake and glycolysis.

AMPK inhibits glycogen synthase (an enzyme that converts glucose to glycogen) and stimulates glycogen phosphorylase (an enzyme that results in the degradation of glycogen to glucose).1,2 5-Aminoimidazole-4-carboxamide-phosphorylase (an enzyme that results in the degradation of glucose to glycogen) and stimulates glycogen phosphorylase activity. AMPK-induced glycogen degradation in perfused rat hearts without inhibiting glycogen synthase and glycogen phosphorylase activities.14 However, repeated AMPK activation increases glycogen content, and the precise roles of AMPK in the glycogen storage process are yet to be fully clarified.1

AMPK and Arrhythmia-Promoting Cardiovascular Disease
A variety of important cardiac disease conditions alter cardiac ion channel and transporter function and promote arrhythmogenesis.15 Metabolic stress plays a central role in the cellular dysfunction caused by conditions such as hypertrophy, heart failure (HF), and myocardial ischemia (Figure 3). By alleviating cellular stress, AMPK plays an important adaptive role and can mitigate complications, presumably including arrhythmogenesis. Interestingly, although there is a strong body of evidence implicating AMPK as protective against arrhythmogenic disease conditions (see below), the actual information available about changes in arrhythmogenesis because of activation or inhibition of AMPK in such conditions is extremely limited.

Cardiac Hypertrophy
Cardiomyocyte hypertrophy is most apparent in response to pressure loads (eg, hypertension and valvular disease), although it occurs with any maintained increase in cardiac load. Cardiac hypertrophy increases metabolic demand, consuming more energy. Relative anoxia results from increased energy needs, as well as impaired coronary blood flow distribution because of altered diastolic transmural pressure gradients, inducing metabolic perturbations. Several studies have shown increased AMPK α-subunit phosphorylation in models of cardiac hypertrophy.16 Uregulated glucose and fatty acid metabolism with AMPK activation increases the availability of energy sources, which may mitigate metabolic stress. AMPK is also involved in downstream signaling processes regulating protein synthesis, such as mammalian target of rapamycin (mTOR), eukaryotic elongation factor-2 (eEF2), and p70S6 kinase (Figure 2).17 These signaling pathways increase protein synthesis and promote hypertrophic growth and proliferation. AMPK inhibits these cascades, countering cardiac hypertrophy.17 AMPK activation mitigates transverse aortic constriction–induced cardiac hypertrophy through inhibition of protein synthetic signaling.1,15 AMPK activation would thus be expected to combat the arrhythmogenic potential inherent in cardiac hypertrophic conditions,20 both by limiting metabolic disturbances caused by hypertrophy and by suppressing hypertrophy itself.

Heart Failure
AMPK prevents the progression from hypertrophy to HF: AMPK α2-subunit–deficient mice show exacerbated transverse aortic constriction–induced hypertrophy and accelerated transition to HF.21 Transition to HF is associated with activation of mTOR signaling, which is responsible for protein synthesis and cell proliferation. AMPK also stimulates autophagy via activation of Unc-51–like kinase that is suppressed by mTOR (Figure 2).22 Malfication of mitochondrial biogenesis is an important component in the development of HF.23 Nuclear receptors and their coactivators, such as estrogen-related receptor α and peroxisome proliferator–activated receptor-γ coactivator 1α, regulate mitochondrial transcripts and stimulate fatty acid oxidation and oxidative respiration.24,25 Activation of AMPK increases expression levels of estrogen-related receptor α: AMPKα2 knockout mice have decreased estrogen-related receptor α expression, whereas constitutively active AMPK increases estrogen-related receptor α expression.24 AMPK activation also stimulates mitochondrial biogenesis via direct phosphorylation of peroxisome proliferator–activated receptor-γ coactivator 1α.25 Both these effects lead to improved mitochondrial function and could, therefore, protect against HF.

Cardiac angiogenesis concomitant with hypertrophy is also critical for slowing the transition to HF: AMPK activation increases the expression of proangiogenic factors, such as endothelial NO synthase and vascular endothelial growth factor.11 Adiponectin has pleiotropic cardioprotective effects and activates AMPK. In adiponectin-deficient mice, impaired AMPK activation accelerates the transition to HF in transverse aortic constriction–induced hypertrophy because of inadequate angiogenesis.26 AMPK decreases endoplasmic stress in endothelial cells and prevents cellular apoptosis in cardiomyocytes.27 AMPK inhibits nicotinamide adenine dinucleotide phosphate-oxidase activation and thereby reduces reactive oxygen species
It must be pointed out that actions of AMPK are not necessarily beneficial in all cardiac failure paradigms. For example, a recent study suggests that AMPK activation may mediate ethanol-induced myocardial hypocontractility via enhanced AMPK-mTOR-Unc-51–like kinase–mediated autophagy.28

Myocardial Ischemia and Reperfusion Injury
AMPK is particularly important during ischemia and ischemia/reperfusion injury. Oxidative metabolism decreases under ischemic conditions, and anaerobic glycolysis predominates. AMPK accelerates glucose metabolism in response to an increased AMP/ATP ratio. The metabolic state of the postischemic myocardium is a critical determinant of myocardial injury and recovery of cardiac function upon reperfusion. Using transgenic mice overexpressing nonfunctional (kinase dead) AMPK, Russell et al29 demonstrated that kinase-dead AMPK hearts fail to augment glucose and fatty acid metabolism during ischemia/reperfusion, manifesting increased myocardial injury.

Substantial energy resources are consumed to incorporate amino acids into protein. AMPK activation limits energy consumption by suppressing protein synthetic signaling pathways, such as eEF-2 and mTOR.30

Although myocardial necrosis is primarily responsible for cell death during ischemia/reperfusion, apoptosis also contributes. The increased myocardial damage in kinase-dead AMPK hearts subjected to ischemia/reperfusion is also because of increased apoptosis.29 The antiapoptotic effect of adiponectin is also mediated by the activation of AMPK.31

Humans with missense mutations in the γ2 regulatory subunit of AMPK (PRKAG2) have hypertrophic cardiomyopathies and frequently manifest arrhythmogenic electrophysiological abnormalities. The pathology caused by the disease-producing PRKAG2 mutations Arg302Gln, Thr400Asn, and Asn488Ile is characterized by preexcitation, atrial fibrillation (AF), progressive conduction system disease, and cardiac hypertrophy.32,33 Mice overexpressing PRKAG2 genes with disease-causing mutations R302Q, N488I, or R531G in the heart recapitulate the phenotype of human PRKAG2 cardiomyopathy.34–36 The effects of these mutations on AMPK function is complex: they seem to enhance basal activity but impair activation because of AMP accumulation.1 Histological findings include an abundance of vacuoles and increased periodic acid-Schiff-positive materials, indicating increased glycogen deposition. Myofiber disarray, typical of hypertrophic cardiomyopathy, is not detected, and interstitial fibrosis is minimal, although the myocytes are enlarged. Ventricular preexcitation and supraventricular tachyarrhythmia are observed in most of the transgenic animals. Patel et al34 demonstrated that the annulus fibrosis, which limits electrical connection between the atria and ventricles, is thinned, stretched, and disrupted in N488I-expressing transgenic mice and that this region contains many vacuolated, glycogen-loaded myocytes. These data suggest that PRKAG2 cardiomyopathy and the associated preexcitation are attributable to a glycogen storage abnormality distinct from hypertrophic cardiomyopathy. Developmental abnormalities lead to failure of formation of a complete annulus fibrosis, preserving atrioventricular muscle bundle connections. The effect of N488I PRKAG2 mutations is specific for AMPK containing α2-subunits; AMPK containing α1-subunits is unaffected.37

Ion Channel Regulation and Other Determinants of Arrhythmia
Figure 4 shows the potential effects of AMPK on a variety of arrhythmia determinants, including ion channels, transporters, and structural factors. The open-state inactivation of cardiac voltage-gated Na+ channels is slowed in mice overexpressing a
This induces a gain in late Na⁺-channel function, increasing action potential duration (APD) and causing early afterdepolarizations, similar to long-QT syndromes caused by SCN5A mutations.38 Thus, basal AMPK activation due to PRKAG2 mutations may be arrhythmogenic by altering Na⁺-channel function. Delayed repolarization is a well-recognized consequence of HF that contributes to arrhythmogenesis; one of the causes may be incomplete Na⁺-channel inactivation due to AMPK activation secondary to HF-induced metabolic stress.

AMPK has potentially significant effects on cardiac K⁺ channels. Ischemic preconditioning involves myocardial ATP-dependent K⁺ (KATP) channels. Mice expressing dominant-negative AMPK α2-subunits (functional AMPK-knockdown) lack preconditioning-induced activation of KATP channels, APD shortening, and cardioprotection.39 The authors provided evidence suggesting that AMPK may be needed to enhance trafficking of KATP channels to the sarcolemma on preconditioning. Phenylephrine-induced cardiac preconditioning also seems to require AMPK-related sarcomembranous KATP-channel activation.40 Although in the case of preconditioning AMPK-related APD abbreviation may contribute to cardioprotection, the same effect could promote the risk of malignant reentrant arrhythmias during acute myocardial ischemia/infarction.

An important recent study showed that AMPK binds constitutively active mutant (T172D) of the AMPK α1-subunit.38 This induces a gain in late Na⁺-channel function, increasing action potential duration (APD) and causing early afterdepolarizations, similar to long-QT syndromes caused by SCN5A mutations.38 Thus, basal AMPK activation due to PRKAG2 mutations may be arrhythmogenic by altering Na⁺-channel function. Delayed repolarization is a well-recognized consequence of HF that contributes to arrhythmogenesis; one of the causes may be incomplete Na⁺-channel inactivation due to AMPK activation secondary to HF-induced metabolic stress.

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An important recent study showed that AMPK binds directly to KATP channels and AMPK activation enhances KATP open probability during metabolic inhibition.41 This observation raises the possibility that low-micromolar AMPK concentrations, as seen in early ischemia and possibly intense exercise, open KATP channels by activating AMPK. This action could be an important contributor to cardioprotection but could also contribute to arrhythmogenesis by reducing APD and promoting reentry.

AMPK has been shown to affect a variety of cardiac-expressed ion channels in noncardiac systems. AMPK phosphorylation of specific sites on Kv2.1 channels causes hyperpolarizing voltage shifts in activation and inactivation gating of neuronal Kv2.1 channels.42 AMPK inhibits K⁺, Ca²⁺ (SK1) Ca²⁺-activated K⁺ channels in human embryonic kidney cells.43 The Kir2.1 subunit that underlies inward-rectifier Iₖ, background outward currents maintaining the cardiomyocyte resting potential is regulated by AMPK when expressed in Xenopus oocytes.44 AMPK reduces Kir2.1 membrane expression and current, apparently by phosphorylating the ubiquitin ligase Nedd4-2.44 A similar type of regulation occurs for the potassium voltage-gated channel, KCNQ1 (KQT-like subfamily, member 1)/potassium voltage-gated channel, KCNE1 (Isk-related family, member 1 channel) that underlies cardiac Iₖ₂. If cardiac Iₖ and Iₖ₂ channels are similarly controlled by AMPK in situ, AMPK activation might downregulate their expression, causing eventual APD prolongation as seen with myocardial ischemia or HF.13 In the case of ischemia, this might lead to a biphasic response as has been observed experimentally,15 with initial APD reduction due to KATP activation, followed by normalization and then APD prolongation due to r_Kr/Ks downregulation.

Ca²⁺ is a central regulator of a wide range of cellular functions, including important cardiac electrophysiological determinants.46 Although relatively little is known about AMPK regulation of cardiac Ca²⁺ handling, there are suggestions that it might be significant. Turdi et al47 examined interactions between aging and AMPK in the control of Ca²⁺ handling and contractility in mice. AMPK kinase-dead young mice showed almost no functional abnormalities other than reduced contractility at rapid rates. Aging reduced AMPK function, expression of the sarcoplasmic reticulum Ca²⁺-uptake pump, sarcoplasmic reticulum Ca²⁺-ATPase-2A (SERCA2A) and contractility, while increasing reactive oxygen species levels and causing cardiomyocyte hypertrophy. Elderly kinase-dead mice demonstrated enhanced mitigation of the aging-dependent changes, as well as reduced systolic [Ca²⁺]-transients and downregulation of the sarcoplasmic reticulum Ca²⁺-ATPase-2A—inhibiting protein phospholamban. Treatment with an AMPK activator, metformin, attenuated physiological aging-induced cardiomyocyte contractile defects. Thus, AMPK contributes to the regulation
of Ca\(^{2+}\) handling and contractile function, and a decrease in AMPK function with aging reduces cardiac contractility.

Ikeda et al\(^4\) developed cardiomyocyte-specific LKB1 knockout mice and demonstrated a crucial role of the LKB1/AMPK axis in maintaining cardiac function. LKB1 knockout mice had attenuated AMPK α2-subunit activation, enhanced protein synthetic signaling (via mTOR and eEF-2), and cardiomyocyte hypertrophy. They also showed impaired contractility in association with decreased phospholamban and sarcoplasmic reticulum Ca\(^{2+}\)-ATPase-2 mRNA/protein expression and had significant atrial dilation along with spontaneous AF.

In addition to direct electrophysiological effects mediated by altered ion channel and transporter function, AMPK might affect arrhythmogenesis indirectly by altering cellular processes that impact indirectly on arrhythmia risk. For example, AMPK-induced reductions in cell proliferation could decrease the likelihood of cardiac tissue fibrosis, an important arrhythmia-promoting change.\(^4\) Similarly, antihypertrophic effects of AMPK could reduce the likelihood of reentrant arrhythmia by preventing increases in cardiac mass.\(^5\)

**Evidence for a Role in Arrhythmias**

Despite important AMPK regulation of many arrhythmia-controlling factors and conditions (Figure 4), data regarding the involvement of AMPK in arrhythmias per se are quite limited. The only 2 clear-cut demonstrations of arrhythmogenesis resulting from primary disturbances in AMPK function are the mouse models of PRKAG2 cardiomyopathy associated with inducible orthodromic AV-reentrant tachycardia\(^6\) and of LKB1 deletion with spontaneous AF.\(^8\) With LKB1 deletion, AF occurs in a context of substantial structural remodeling and is not necessarily directly attributable to AMPK dysfunction.

Other observations suggest a role of AMPK in controlling arrhythmogenesis but are not definitive. Barth et al\(^7\) found a relationship between metabolic alterations and permanent AF in human cardiomyocytes; transcripts involved in carbohydrate metabolism were significantly upregulated in atrial tissues from AF patients, whereas transcripts involved in fatty acid metabolism were downregulated. Recent metabolomic and proteomic analyses in human AF also demonstrate significant changes in the atrial enzymes and metabolites responsible for glycolysis and fatty acid oxidation, consistent with metabolic stress.\(^5\) A lower ratio of glycolytic/lipid metabolism end products was associated with early onset of postoperative AF, suggesting that metabolic disturbances increase AF vulnerability. This notion is supported by experiments showing that the inhibition of glycolysis promotes the occurrence of spontaneous AF in Langendorff-perfused rat hearts.\(^5\) In an electrically maintained AF model in goats, phosphocreatine decreased by 60% in atrial myocytes within 1 week, suggesting increased energy demand and expenditure during the early phases of AF.\(^5\)

It is well known that HF promotes atrial and ventricular arrhythmogenesis.\(^1\) Cha et al\(^10\) demonstrated that dogs with

![Figure 5. Metabolic stress–related mechanisms in atrial fibrillation (AF) and possible role of AMP-activated protein kinase (AMPK).](http://circep.ahajournals.org/) Increased cellular workload during the rapid atrial activation in AF increases energy demand and expenditure. The consequent metabolic stress limits the availability of ATP that controls cellular integrity and channel/transporter protein function. AF-induced dysregulation of ion channels, such as \(I_{Na,L}\) and \(I_{Ca,L}\), causes action potential duration (APD)/wavelength (WL) shortening and conduction velocity (CV) slowing, which stabilizes reentrant mechanisms maintaining AF. Abnormal Ca\(^{2+}\) handling causes hypocontractility and atrial dilatation that contributes to the AF substrate, as well as triggered arrhythmia mechanisms. In addition, enhanced production of reactive oxygen species (ROS) because of metabolic stress damages cellular macromolecules to cause AF-promoting dysfunction. AF-induced metabolic stress reduces the ratios of AMP/ATP and ADP/ATP, activating AMPK. AMPK activation should increase energy production (fatty acid/glucose metabolism) and limits energy consumption (protein synthesis), thereby counteracting the AF-induced metabolic stress. AMPK might also regulate ion channel function via direct phosphorylation. Changes in **black** have been observed experimentally; those in **gray** have not yet been examined but would be expected to occur. RyR2 indicates ryanodine receptor type-2; NCX, Na+/Ca\(^{2+}\)-exchanger; SERCA2, sarcoplasmic reticulum Ca\(^{2+}\)-ATPase; PLB, phospholamban; Tn-I, troponin-I; MyBP-C, myosin binding protein C; mTOR, mammalian target of rapamycin.
dilated cardiomyopathic phenotypes caused by ventricular tachypacing have important defects in atrial bioenergetics, with depletion of ATP and creatine kinase, and that the propensity for AF is inversely related to atrial cellular ATP concentration. Another study in the same model showed profound changes in the expression of metabolic proteins and metabolites, with increased ADP/ATP ratio and a shift from glycolysis to α-ketoacid metabolism after 2 weeks of ventricular tachypacing.\(^57\) The glycolytic system was upregulated at 24 hours of ventricular tachypacing, suggesting an early response to increase energy output in the face of increased demands, with longer-term energy-preserving adaptations.\(^57\)

There is thus extensive evidence for a role of metabolic stress in AF. Figure 5 shows a schema illustrating the potential involvement of metabolic abnormalities and AMPK in AF. AF induces metabolic stress by virtue of an increased workload due to a much increased atrial rate. Biochemical derangements resulting from metabolic stress alter ion channel function in ways that promote arrhythmia induction and maintenance, creating a positive feedback circuit. AMPK activation would be expected, based on the observed increase in ADP/ATP ratio\(^57\) and a likely concomitant rise in the AMP/ATP ratio. AMPK-induced phosphorylation would be expected to increase energy availability and reduce demands. If so, modulation of the AMPK system might provide a useful therapeutic target, and failed or deficient AMPK activation could promote AF in some cases.

AMPK may also be a mediator of antiarrhythmic drug properties. Resveratrol has important AMPK-activating properties\(^69,58\) and is antiarrhythmic.\(^59\) Although the compound may have direct ion channel effects, it is conceivable that AMPK activation contributes to its beneficial effects on arrhythmias.\(^59\)

**Conclusions**

Emerging evidence demonstrates a close relationship between metabolic disturbances and cardiac electrophysiology and suggests the ability of AMPK to regulate a wide range of determinants of electrophysiological function and arrhythmogenesis. However, relatively little work has been done to address directly the participation of AMPK in cardiac electrical function and arrhythmias. Much more research is required to complete our understanding of the susceptibility of cardiac ion channels and transporters to modulation by AMPK activation, as well as to understand the involvement of AMPK in controlling arrhythmogenesis in pathological states. AMPK activation may play a protective role in some contexts and a proarrhythmic role in others—clarification of its consequences in specific contexts will be important. Present antiarrhythmic drug therapy is limited by poor efficacy and significant adverse effect risk: improved mechanistic understanding of arrhythmias may hold the key to ameliorating therapeutic potential.\(^60,61\) A better appreciation of the role of this important enzyme in controlling electrical activity in the normal and diseased heart might lead to important new mechanistic insights and potentially to new therapeutic opportunities.

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**References**

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