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AMP-Activated Protein Kinase: A Stress-Responsive Kinase with Implications for Cardiovascular Disease

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Abstract

AMP-activated protein kinase (AMPK) was initially viewed as energy sensor and activated by increased intracellular concentrations of AMP following nutrient deprivation. Physiological or pathological stimuli that deplete cellular energy activate AMPK which coordinates a cellular program that limits further ATP depletion and promotes compensatory changes that maintain cellular ATP levels. Recent studies revealed novel roles of AMPK independent of energy status, thereby increasing our understanding of multi-functional roles of AMPK in cells important in pathogenesis of cardiovascular diseases. This enzyme represents an attractive therapeutic target for vascular disease treatment in the future.

Keywords

AMPK; stress; cardiovascular disease

Introduction

The AMP-activated protein kinase (AMPK) plays a critical role in censoring energy status in eukaryotic cells. This kinase is highly conserved amongst organisms and is classically activated under conditions of nutrient deprivation resulting in an increase in the AMP/ATP ratio [1]. More recently evidence indicates that AMPK activation is elicited by diverse signals such as hormones and cytokines that are secreted in response to environmental stress. Since many cardiovascular pathologies (*e.g.* hypertension, left ventricular hypertrophy, heart attack, stroke, etc.) represent an environmental stress and evoke “injury” signals in vascular tissues and the heart, it is not surprising that AMPK may be activated and have a modulatory role in many of these cardiovascular conditions. Thus, the aim of the present review is to discuss the role of AMPK in common cardiovascular diseases.

The “Traditional” Role of AMPK

The AMPK is conserved through species ranging from simple yeast to complex mammalian cells. Initially, SNF1 (for sucrose nonfermenting) was identified as a genetic locus shown to play a central role in carbon catabolite repression in yeast *Saccharomyces cerevisiae* [2]. The

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SNF1 gene was then determined to encode a protein kinase [3;4] that proved similar to the cRKIN1 gene product (from rye) and cRKIN1 could “rescue” the SNF1 mutation [5], indicating they serve overlapping functions. Finally, the mammalian AMPK was identified as the homolog to yeast SNF1 gene and plant RKIN1, thereby establishing this family of kinases as critical for energy homeostasis.

In mammals, AMPK is a heterotrimeric complex consisting of α , β , and γ subunits [6]. The α subunit of AMPK is the catalytic center and has two isoforms, $\alpha 1$ and $\alpha 2$ that are phosphorylated at threonine 172 upon enzyme activation. The AMPK $\alpha 2$ is mainly located in muscle, brain, and liver that have high energy demands. In contrast, AMPK $\alpha 1$ is relatively ubiquitously distributed in tissues such as the pancreas, leukocytes, smooth muscle and endothelial cells. The β subunits ($\beta 1$ and $\beta 2$) contain a glycogen-sensing domain required for kinase function and substrate definition. The γ subunits ($\gamma 1$, $\gamma 2$, and $\gamma 3$) contain 2 regulatory binding sites for AMP and ATP [7].

Physiological or pathological stimuli that deplete cellular energy levels such as prolonged exercise, metabolic poisoning, heat shock, oxidative stress, hypoxia, ischemia or nutrient deprivation, result in an increased AMP/ATP ratio that, in turn, activates AMPK. The activation of AMPK coordinates a cellular program that limits further ATP depletion and promotes compensatory changes that maintain cellular ATP levels. Typically, energy consuming processes (*e.g.* synthesis of glycogen, fatty acids, and cholesterol) are inhibited and catabolic processes producing ATP are stimulated. These aspects have recently been reviewed in detail elsewhere [1;8;9]. As one might expect, AMPK is essential for normal cellular function and compound gene deletions of the catalytic isoforms are lethal, whereas single isoform deletions are viable, albeit with some pathology.

AMPK Activation Independent of the AMP/ATP ratio

There has been considerable interest in AMPK activation independent of the AMP/ATP ratio. Toyoda and colleagues demonstrated in skeletal muscle that oxidative stress activated AMPK and increased glucose transport independent of change in the conventional parameters of AMPK activation such as AMP and AMP/ATP ratio [10]. Recently, it has been shown that AMPK is activated upon hypoxia by endogenous mitochondrial reactive oxygen species (ROS) as a consequence of nitric oxide (NO^{*})-mediated inhibition of cytochrome c oxidase in endothelium [11;12]. This mechanism for AMPK activation without change in ATP, AMP, or ADP is important for cellular responses to hypoxia [13]. Additional stimuli including statins, peroxynitrite, adiponectin, leptin, metformin, and calmodulin-dependent protein kinase kinase II (CaMKKII) were shown to activate AMPK independent of changes in AMP/ATP ratio. Recent additions to agonists and agents activating AMPK are summarized in Table. The activation of AMPK by mitochondrial ROS is involved in cell proliferation, counteracting oxidative stress and apoptosis in endothelial cells. In addition, AMPK was shown to be activated by IL-6 under exercise and by TNF α under conditions of insulin resistance. Thus, AMPK activation has been observed in response to various environmental stresses. These stress responses suggest that AMPK should have some adaptive influences in the cardiovascular system.

AMPK in Diabetes and Hypertension

Given its role in stress responses, there has been considerable interest in AMPK in the adaptation of cardiovascular tissues to pathologic conditions. The vascular endothelium, typically a key determinant of vascular homeostasis, is particularly prone to injury and dysfunction in the setting of cardiovascular disease. This dysfunction is observed in diabetes, and is associated with diminished bioactivity of nitric oxide (NO) and excess vascular ROS. In this setting, AMPK activation with either AICAR or metformin upregulated both uncoupling

protein-2 (UCP-2) mRNA and UCP-2 protein that significantly attenuated oxidative stress in diabetes [14]. In another study, in vivo activation of AMPK normalized endothelial function in diabetic animals, in part by preserving GTP-cyclohydrolase, an enzyme essential for normal NO bioactivity [15]. Diabetic rats treated with cilostazol, a selective inhibitor of phosphodiesterase 3, also exhibit normalization of endothelial function that was linked to AMPK activation producing increased endothelial nitric oxide synthase (eNOS) activity and NO production [16]. Another aspect of endothelial dysfunction in diabetes is the upregulation of adhesion molecules that contribute to the trafficking of inflammatory cells into the vascular wall. The activation of AMPK via carbon monoxide attenuates intracellular adhesion molecule-1 upregulation due to hyperglycemia [17].

The implications of AMPK have also been examined in the endothelial dysfunction associated with hypertension. Chronic AMPK activation with AICAR decreased blood pressure in rats displaying features of the insulin resistance syndrome [18]. Consistent with a role of AMPK in vasomotion, Goirand et al. showed that AMPK activation induces vasodilatation and blood flow regulation in wild-type mice and this effect was abolished AMPK α 1 knockout mice [19]. Our laboratory's work examined the role of AMPK in more generalized stress responses. Chronic activation of AMPK in vivo attenuated ROS-mediated c-Jun N-terminal kinase activation and endothelial dysfunction in response to angiotensin II. The effect was abrogated in mice lacking the endothelial isoform of AMPK α 1 or peroxisome proliferator gamma coactivator-1, a known target of AMPK that controls mitochondrial biogenesis [20].

AMPK in Atherogenesis and Inflammation

Vascular smooth muscle cell proliferation is involved in the pathogenesis of both atherosclerosis and arterial injury. The activation of AMPK inhibits angiotensin II-induced smooth muscle proliferation and the neointimal formation typically associated with femoral arterial injury [21]. This inhibition of smooth muscle cell proliferation also applies to other agonists as platelet-derived growth factor-induced vascular smooth muscle cell proliferation and migration is inhibited by berberine in an AMPK-dependent manner [22]. In that study, AMPK activation resulted in phosphorylation of p53 and increased protein levels of Cdk inhibitor p21^{Cip1}, thereby inhibiting cell cycle progression.

The oral hypoglycemic drug, metformin, is known to activate AMPK. In this regard, metformin-induced AMPK activation prevents endothelial cell NF- κ B activation in response to inflammatory cytokines. As a consequence, cytokine-stimulated expression of adhesion molecules such as VCAM-1, ICAM-1, E-selectin, and MCP-1 are inhibited [23]. As one might expect, AMPK activation likewise inhibits TNF α -stimulated leukocyte adhesion to human aortic endothelial cells and ICAM-1 mediated migration of lymphocytes across primary rat and human microvascular endothelial cells [24;25]. These findings are significant, as one would expect that inhibition of inflammation should have a favorable impact on atherosclerosis. As yet, there have not been published studies demonstrating the role of AMPK in atherosclerosis.

AMPK in Myocardial Injury

AMPK has emerged as a promising target for protection of the heart from ischemic injury, pathological hypertrophic growth, and heart failure. Activation of AMPK appears important for compensation during energy imbalance conditions induced by ischemia/reperfusion in the heart [26]. Studies showed that glucose transport was increased and glycolytic ATP production was enhanced by activation of the enzyme 6-phosphofructo-2-kinase in the ischemic heart [27]. Both catalytic α 1- and α 2-isoforms of AMPK containing regulatory γ 1- or γ 2-isoforms were activated and γ 1 isoform complexes were responsible for most of the AMPK activity in the ischemic heart [28]. AMPK promotes fatty acid oxidation by phosphorylating ACC,

lowering the concentration of malonyl-CoA, leading to activation of carnitine palmitoyltransferase-1 and free fatty acid oxidation in postischemic reperfused heart [27]. Indeed, AMPK-deficient mice demonstrated impairment in postischemic fatty acid oxidation [29]. In the setting of systolic pressure overload, left ventricular hypertrophy ensues and AMPK α 2 knockout mice exhibit significantly increased overload-induced ventricular hypertrophy and decreased left ventricular ejection fraction [30]. AMPK γ 2 mutations are associated with hypertrophic cardiomyopathy in human [31]. Using the converse approach, another group showed that preincubation of cardiomyocytes with the AMPK stimulator AICAR prevented angiotensin II-induced cardiomyocyte hypertrophy [32]. *In vivo*, pacing-induced heart failure was significantly improved by AMPK activation, possibly via eNOS stimulation, resulting in decreased apoptosis and improved cardiac function in these failing canine hearts [33]. Indeed, previous report that isolated hearts of AMPK-deleted mice show increased apoptosis and dysfunction after ischemia/reperfusion supports the role of AMPK in regulation of apoptosis which is an important mechanism of heart failure [29;34].

Thus, it is clear that AMPK plays a role in the myocardial adaptation to stress associated with ischemia/reperfusion, pressure overload, and heart failure. Collectively, four possible mechanisms have arisen to explain AMPK-mediated protective effects on the myocardium [33]. These include: a) enhancement of NO production; b) improvement in insulin resistance; c) metabolic effects of AMPK activation; and d) the antifibrotic effect of metformin. However, the exact roles of each factor in improvement in the pathophysiology of heart failure remain to be determined and will undoubtedly be the subject of future investigation.

Perspectives

From the information in the preceding paragraphs, it is clear that AMPK is one of many stress responses in cardiovascular tissues. Chronic activation of AMPK appears to confer adaptive resistance to stress in a number of conditions, including endothelial dysfunction, response to arterial injury, and myocardial injury. The precise mechanisms whereby AMPK confers a multitude of salutary effects are not clear at the moment, but may be linked to the upregulation of mitochondrial biogenesis and antioxidant defenses. Continued investigation will be needed to develop new strategies that exploit AMPK and its downstream targets as treatment(s) for cardiovascular diseases.

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Figure.

Schematic mechanisms for AMPK implication in cardiovascular disease. AMPK is activated by a number of stimuli and its downstream actions have implications for cardiovascular disease. Its effects are pleiotropic in that some pathways are stimulated and others are inhibited. CO, carbon monoxide; AICAR, 5-Aminoimidazole-4-carboxamide riboside; UCP-2, uncoupling protein-2; GTPCH I, GTP-cyclohydrolase I; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; PGC-1 α , peroxisome proliferator gamma coactivator-1 α ; SMC, smooth muscle cell; GLUT4, glucose transporter 4; PFK-2, 6-phosphofructo-2-kinase; ATP, adenosine triphosphate; ACC, acetyl-CoA carboxylase; CPT-1, carnitine palmitoyltransferase-1.

Table

AMPK stimulation or inhibition independent of an increase in AMP/ATP ratio. PLC, phospholipase C; CaMKK, calmodulin-dependent protein kinase kinase; PKC, protein kinase C; PP2A, protein phosphatase 2A; MIF, migration inhibitory factor. (+), stimulatory; (−), inhibitory.

Agonists	Signaling mediators	Regulation of AMPK	Reference
hypoxia	mitochondrial ROS	(+)	[13;35]
adiponectin	LKB-1, PLC, CaMKK	(+)	[36]
statin	LKB-1, PLC, CaMKK; PKCζ	(+)	[37]
peroxynitrite	PKCζ, LKB-1	(+)	[38]
metformin	PKCζ	(+)	[39]
palmitate	PP2A	(−)	[40]
ischemia	MIF, CD74	(+)	[41]