AMP-Activated Protein Kinase Conducts the Ischemic Stress Response Orchestra

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The heart is subjected to physiological stress in normal individuals during exercise and to pathological stress in patients with ischemic disease, ventricular pressure, or volume overload. How the heart responds depends on the type, intensity, and duration of the stress. Just as extrinsic physiological reflexes are activated when cardiac output falls, internal molecular sensors respond to changes in physiological parameters within cardiac cells. These specialized molecules sense perturbations in oxygen tension, cell stretch, pH, membrane potential, oxidative state, and intracellular energy stores, with the latter particularly pertinent to this discussion.

The present article will focus on the AMP-activated protein kinase (AMPK), a molecular stress response pathway that is activated by increases in the intracellular concentration of AMP. AMP is not to be confused with cAMP, a molecular signal produced during stress by catecholamine-induced β-adrenergic stimulation. The AMPK pathway has received a great deal of attention because of its potential importance in the ischemic heart, diabetes, and cancer. Several recent reviews have summarized scientific discoveries related to AMPK and can provide the interested reader with additional insights into the field. The present article will strive to provide a perspective that is accessible to the clinician with an interest in contemporary basic science research. It is hoped that the reader will develop an understanding of how AMPK functions in the heart to orchestrate the cellular response to ischemic stress.

AMP and Cellular Energy Stress

Cells have evolved elaborate mechanisms to protect themselves against changes in their environment. In the heart, one of the most important forms of cellular stress is energy depletion from ischemia. ATP is the primary energy source for contractile proteins, ion pumps, and many enzymes. Normally, energy production and utilization are tightly coupled in the heart. When ATP generation from substrate metabolism fails to keep pace with ATP utilization, the intracellular concentration of ADP increases. Two molecules of ADP are converted to 1 molecule each of ATP and AMP through the action of the enzyme adenylate kinase. This reaction not only helps to regenerate ATP as an energy source but also forms AMP. AMP serves as an internal signal that the cell is under metabolic stress (Figure 1). Normally, AMP is present in substantially lower concentrations than ATP. Even a small amount of ATP breakdown significantly increases the concentration of AMP. Thus, AMP is a very sensitive and early indicator of compromised energy availability.

How does AMP work as a molecular signal? AMP directly regulates a limited number of enzymes that are involved in metabolic pathways responsible for cellular energy generation (Figure 1). For instance, AMP activates glycogen phosphorylase, which releases stored glucose from glycogen, an important source of energy when fuel oxidation is impaired during ischemia. AMP similarly activates the enzyme phosphofructokinase-1 (PFK-1). PFK-1 acts as a metabolic gatekeeper, regulating the entry of glucose into glycolysis. However, the molecular signaling role of AMP is dramatically extended by activation of the AMPK pathway. Because many more proteins are regulated by AMPK than contain specialized AMP-binding sites, the ability of AMP to signal energy compromise is greatly enhanced.

AMPK is a protein kinase that has taken center stage in metabolic regulation over the last decade. Protein kinases are specialized enzymes that transfer phosphate groups from ATP to amino acids on specific target proteins. The phosphorylation of even a single amino acid can induce conformational changes in enzymes, ion channels, and regulatory and structural proteins that alter their function. AMPK was first identified 20 years ago as a protein kinase that was responsive to changes in the concentration of AMP and modulated the activity of the enzymes acetyl-CoA carboxylase and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. Phosphorylation of acetyl-CoA carboxylase inhibits its action to synthesize malonyl-CoA, a small molecule that functions as an activator of fatty acid synthesis in the liver and an inhibitor of fatty acid oxidation in the heart. Phosphorylation of HMG-CoA reductase inhibits cholesterol biosynthesis. The physiological significance of this action is not fully understood, but AMPK might contribute to the drop in cholesterol levels observed in patients during acute coronary syndromes. It is interesting that statins also activate AMPK, which might augment their direct action to inhibit HMG-CoA reductase and lower cholesterol levels.
AMPK has come to be known as a molecular “fuel gauge” or “metabolic sensor.” It phosphorylates a variety of proteins including metabolic enzymes, transcription factors, and ion channels. In many cases, these actions curtail the use of ATP and accelerate metabolism to generate more ATP. AMPK thus has the potential to influence a broad array of cellular pathways that regulate energy utilization and production. AMPK might be thought of as the conductor of an orchestra composed of diverse players that mediate stress responses in the cell, as will subsequently be enumerated.

Molecular Structure and Function of AMPK

AMPK is actually a complex of 3 different proteins, which are referred to as the α, β, and γ subunits (Figure 2). Each subunit has a distinct structure and function; their coordinated interaction is necessary for changes in the cellular environment to modulate the activity of the AMPK complex. The α subunit contains the catalytic domain of the enzyme, which transfers a phosphate group from ATP to serine (and occasionally threonine) sites in target proteins. The β subunit provides a structural bridge between the other subunits and also contains a specialized sequence that binds to glycogen. High concentrations of glycogen are present when fuel supply is abundant, and therefore it is not surprising that glycogen depletion might also contribute to activation of AMPK in the heart during ischemia or exercise. The γ subunits have an important regulatory function because they contain the critical binding sites, which enable AMP to activate and ATP to inhibit the AMPK complex.

The α, β, and γ subunits each have multiple isoforms, with minor differences in their amino acid sequences, varying according to cell type. In cardiomyocytes, the α2 isoform is more abundant than the α1, which is the sole isoform in endothelial cells. The heart contains the γ1 and γ2 isoforms but lacks the γ3 isoform that is expressed in skeletal muscle. Small structural differences among these isoforms appear to affect AMPK sensitivity to activation, its location within the cell, and the proteins that it regulates. For instance, the α2 isoform is more sensitive than the α1 isoform to changes in the intracellular AMP concentration. This may explain the observations that both the α1- and α2-containing complexes are activated during ischemia, but the less intense stress of exercise primarily activates α2. AMPK complexes are found predominantly in the cytoplasm, where they modulate energy generating and consuming pathways. However, complexes containing the α2 isoform are also present in the nucleus, where they likely modulate gene expression.

Mechanisms of Activation of AMPK

In the heart, AMPK is activated by increases in the intracellular concentration of AMP or ADP (Figure 2). AMP induces a conformational change, which directly enhances the activity of AMPK. AMP binding also exposes an important regulatory site (Thr172) in the catalytic α subunit and promotes its phosphorylation, which substantially increases AMPK activity. AMP binding renders AMPK less susceptible to the action of protein phosphatases that remove the phosphate from the Thr172 site and deactivate AMPK. ATP normally blunts these effects of AMP, so that the fall in ATP that occurs during ischemia augments AMP activation of the AMPK complex.

Upstream enzymes that phosphorylate AMPK and modulate its activity are referred to as AMPK kinases. The tumor suppressor protein LKB1 was the first such kinase discovered. Mutations in the human LKB1 gene cause the Peutz-Jeghers syndrome, an inherited disorder characterized by gastrointestinal polyps and malignancy. The link between LKB1 and AMPK was the first hint that the AMPK pathway might protect against the development of cancer. Recent studies also have identified LKB1 mutations in lung adenocarcinomas. LKB1 has a number of additional interesting biological actions, such as directing the intracellular movement of proteins in a manner that determines cell polarity in epithelial cells. It also prevents programmed cell death or apoptosis, a process that plays a role in organ development, heart failure, and ischemic injury. LKB1 has an
important role in regulating AMPK in the heart, where the absence of LKB1 prevents the activation of AMPK complexes containing the major α2 isoform during ischemia.36

Although AMPK is an internal energy sensor, it is becoming clear that additional factors influence AMPK activation, such as the hormones adiponectin37 and insulin.38,39 Adiponectin is an adipocyte-derived hormone, which activates AMPK and has a protective effect against ischemic injury in the heart.37 Conversely, insulin inhibits AMPK activation.38,39 which makes teleological sense because insulin levels increase in response to nutrient excess. Insulin and AMPK have a number of counteracting metabolic effects; insulin promotes glycogen, triglyceride, and protein synthesis, while AMPK inhibits these energy-consuming processes.6,40

**Cardiac AMPK and Exercise**

Because AMPK is a fuel sensor that regulates energy generating metabolic pathways, one might anticipate that it would have a physiological role to modulate the response to exercise. Indeed, exercise stimulates cardiac AMPK activity.17,22 and activated AMPK accelerates the metabolism of fatty acids and glucose in the heart.23,41,42 However, the extent to which activated AMPK is essential to energy generation during exercise remains uncertain. Animals with genetic alterations that partially inhibit cardiac AMPK appear to exercise well.22 These findings suggest that additional molecular mechanisms might also trigger metabolic adaptation during exercise.

**Actions of Activated AMPK in the Ischemic Heart**

Activated AMPK has a number of diverse actions during ischemia. AMPK is known to modulate energy generating metabolic pathways, cellular protein synthesis, gene expression, ion channel activity, and the function of specialized organelles in the ischemic heart (Figure 3). In some cases, the specific molecules that are directly phosphorylated by AMPK have been identified. In other cases, AMPK has indirect actions that are mediated through its interaction with additional signaling pathways, such as the nitric oxide pathway.43,44 These latter observations are consistent with the evolving concept that intracellular signaling pathways function as interwoven networks, which modulate each other.

One of the fundamental responses to ischemia is to increase cellular glucose metabolism. In the heart, the first step in glucose utilization is the transport of glucose across cell surface membranes into the cytosol, where it is actively metabolized. Cardiac glucose transport is mediated by specific glucose transporter proteins.45 GLUT4 is the primary cardiomycyte transporter responsible for glucose uptake in the ischemic heart.46 When subjected to stress, the heart recruits GLUT4 transporters from intracellular storage membranes to the cell surface, where they are physiologically active.45 We now know that activated AMPK provides the molecular signal that triggers GLUT4 recruitment in the ischemic heart.16,47 (Figure 4). The GLUT4 transporter is not phosphorylated by AMPK, and the mechanism by which activated AMPK modulates GLUT4 recruitment in the ischemic heart is not fully understood. Activated AMPK appears to stimulate GLUT4 recruitment in part through its interactions with other signaling pathways.44,48 However, the amount of GLUT4 on the cell surface is also determined by the rate of recycling of transporters back into intracellular storage membranes. Transporter recycling is also inhibited by activated AMPK.49 Thus, AMPK regulates the fundamental movement of glucose transport molecules within the cell and therefore is critical to the activation of glucose metabolism in the ischemic heart.

AMPK has a central role in the regulation of major energy-generating metabolic pathways during ischemia as well as during postischemic reperfusion. The actions of activated AMPK in the ischemic heart are probably best understood by first summarizing a few facts about heart metabolism. Under fasting conditions, the normal heart generates ATP primarily from the oxidation of fatty acids, which are delivered to the heart as fatty acids bound to albumin or contained within triglyceride-rich lipoprotein particles. Glucose is an important fuel for the heart after carbohydrate-
containing meals, which increase insulin levels and decrease fatty acid concentrations in the plasma. Fuel metabolism in the heart changes dramatically during myocardial ischemia because oxidative metabolism is reduced in proportion to the lack of oxygen delivery. However, ischemia increases the metabolism of glucose through the glycolytic pathway, which generates ATP despite the lack of oxygen. Activated AMPK in the ischemic heart stimulates the enzyme PFK-2 to synthesize fructose 2,6-bisphosphate, an activator of PFK-1. As previously mentioned, PFK-1 is a critical regulator of glycolysis. Thus, activated AMPK stimulates both glucose transport into the cell and glycolysis, promoting ATP generation during ischemia.

AMPK also has important influences on metabolism in the reperfused heart after ischemia. After coronary reperfusion, metabolism in the postischemic myocardium is an important determinant of the recovery of contractility and the degree of ischemic injury. In experiments studying isolated hearts, AMPK activity typically remains elevated during postischemic reperfusion. As in the ischemic heart, activated AMPK is also responsible for the enhanced glucose uptake that occurs during early reperfusion. As already mentioned, activated AMPK also inhibits acetyl-CoA carboxylase, the enzyme responsible for the synthesis of malonyl-CoA. Malonyl-CoA is a potent inhibitor of the mitochondrial enzyme carnitine palmitoyltransferase-1, which facilitates fatty acid entry into mitochondria for oxidation. By reducing the synthesis of malonyl-CoA, AMPK thus enhances mitochondrial fatty acid oxidation during postischemic reperfusion.

Activated AMPK also promotes heart fatty acid oxidation by stimulating the entry of fatty acids into the cardiomyocyte via the cell membrane transport protein CD36. Analogous to its effect on glucose transporters, activated AMPK stimulates the recruitment of CD36 from intracellular storage membranes to its active site on the cell surface. Additionally, activated AMPK facilitates the uptake of fatty acids from triglyceride-containing lipoprotein particles, which are an important fuel source for the heart. The enzyme responsible for extracting fatty acid molecules from triglycerides is lipoprotein lipase (LPL). LPL is synthesized by cardiomyocytes but moves to the capillary endothelium, where it interacts with lipoproteins in the blood. Activated AMPK stimulates the movement of LPL from cardiomyocytes to endothelial cells. Thus, activated AMPK has several physiological effects that act in concert to promote fatty acid oxidation in the reperfused heart (Figure 4).

Fatty acid oxidation plays an important role in generating energy in the postischemic heart. However, excessive fatty acid oxidation during reperfusion also impairs glucose oxidation because of inhibition of the mitochondrial enzyme pyruvate dehydrogenase. An imbalance between glucose uptake and glucose oxidation results in persistent lactate production that can perpetuate intracellular acidosis and potentially promote calcium overload after ischemia. Particularly under conditions of fatty acid excess, this action of AMPK can have detrimental effects in the reperfused heart.

AMPK and Energy Stores in the Ischemic Heart

The 2 major high-energy storage molecules in the heart are ATP and creatine phosphate. As already mentioned, ATP is the energy source for contractile proteins, ion pumps, and many enzymes. Creatine phosphate transfers its high-energy phosphate molecule to ADP and regenerates ATP when the energy source for contractile proteins, ion pumps, and many enzymes. ATP and creatine phosphate. As already mentioned, ATP is the energy source for contractile proteins, ion pumps, and many enzymes. Creatine phosphate transfers its high-energy phosphate molecule to ADP and regenerates ATP when energy supply in the ischemic heart. In the absence of normal AMPK activation, both ATP and creatine phosphate are more severely depleted after ischemia/reperfusion. These findings have led to the concept that AMPK is an energy guardian in the ischemic heart.

AMPK functions as an energy guardian because it lessens the imbalance between ATP production and consumption during ischemia/reperfusion. Although much of the preceding discussion has focused on its role to enhance energy production, an important effect of activated AMPK in the ischemic heart is to conserve energy. AMPK activation is known to inhibit the energy-consuming processes required to synthesize large macromolecules, such as glycogen, triglycerides, and proteins. Indeed, turning off the synthesis of new proteins may be an important effect of activated AMPK in the ischemic heart. Although contraction is the major determinant of ATP consumption in the normal heart, contractile activity quickly diminishes in the ischemic myocardium, leaving protein synthesis as an important component of residual myocardial energy expenditure. The addition of each amino acid onto a nascent protein requires energy in the form of ATP. Cellular proteins undergo a perpetual process of synthesis and degradation, which requires significant energy expenditure. Thus, the action of activated AMPK to inhibit protein synthesis conserves ATP that can then be utilized for more vital cellular functions, which might promote short-term survival during ischemia.

How does activated AMPK inhibit protein synthesis? AMPK interacts with an elaborate molecular network, which governs the machinery responsible for protein synthesis (Figure 5). Each stage of protein synthesis is highly regulated,
from initiating the translation of the messenger RNA templates that code for the protein to final processing of the protein. Activated AMPK slows the addition of amino acids onto nascent proteins by inactivating a protein called eukaryotic elongation factor-2 (eEF-2). AMPK directly activates eEF-2 kinase, which in turn inactivates eEF-2. Thus, AMPK activation slows the incorporation of amino acids into new proteins.

Activated AMPK also inhibits protein synthesis by inactivating the well-known protein complex called mammalian target of rapamycin (mTOR). The mTOR complex is a sensor of cellular nutrient status. It is activated when amino acids are readily available to the cell, as well as by insulin and other growth factors. Activated mTOR stimulates protein synthesis and cell growth. Rapamycin in drug-eluting stents inhibits mTOR and thus blocks vascular smooth muscle cell proliferation. How does activated AMPK regulate the mTOR complex? AMPK inhibits mTOR indirectly by activating the tuberous sclerosis complex tumor suppressor protein TSC2. Human mutations in TSC2 cause hamartomas, presumably because of unrestrained protein synthesis and cell proliferation. AMPK activation of TSC2 inhibits mTOR activity. Because mTOR normally activates the ribosomal S6 kinase and eukaryotic initiation factor-4, which enhance protein synthesis, AMPK inhibits protein synthesis. Thus, AMPK activation turns off several components of the protein synthesis machinery and through this mechanism conserves energy under the duress of ischemia (Figure 5).

AMPK and Ischemic Injury
AMPK activation has a number of important physiological effects that appear to prevent myocardial injury during ischemia. Hearts from mice with genetically inactivated AMPK show impaired recovery of left ventricular contractile function after ischemia and reperfusion. These hearts also demonstrate significantly increased myocardial necrosis after ischemia and reperfusion, indicating that AMPK protects against cell death. Although these findings support the contention that AMPK is cardioprotective in isolated hearts, many additional factors are operative in the intact organism that can influence the action of AMPK. Ongoing research should clarify whether AMPK has a protective effect in clinically relevant animal models of regional ischemia. The results of these studies will shed light on whether AMPK activators might warrant consideration for use in the treatment of myocardial ischemia in the future.

Myocardial necrosis is the primary mechanism responsible for cell death from ischemia. However, a small amount of apoptosis or programmed cell death also is induced by ischemia/reperfusion. When AMPK activation is impaired, apoptosis is substantially increased in hearts subjected to ischemia/reperfusion. AMPK activation also contributes to the antia apoptotic effects of the hormone adiponectin. Thus, it appears that activated AMPK is also protective in the heart by limiting apoptosis during ischemia/reperfusion.

AMPK and Ischemic Preconditioning
Recent evidence suggests that AMPK might also protect against injury by promoting ischemic preconditioning. Ischemic preconditioning is an interesting phenomenon through which short periods of ischemia render the heart less susceptible to injury during subsequent more prolonged ischemic insults. Ischemic preconditioning is sometimes used to prevent myocardial injury during off-pump coronary bypass surgery. Short periods of ischemia are induced before occluding the coronary artery in order to perform the distal anastomosis of the bypass graft without injury to the myocardium. AMPK is activated by short durations of ischemia as well as by experimental preconditioning. AMPK has been shown to induce preconditioning in isolated cardiomyocytes and to prevent hypoxic injury. The degree to which AMPK activation is either required or sufficient to induce preconditioning in the intact heart is uncertain but warrants further investigation because of its potential clinical application in preventing ischemic myocardial injury.

The molecular mechanisms responsible for ischemic preconditioning are complex. However, one mechanism through which activated AMPK might induce ischemic preconditioning is by activating ATP-sensitive potassium channels. AMPK stimulates the movement of these channels from storage membranes to the cell surface membranes, where they are physiologically active. These channels shorten the action potential and prevent calcium overload during reperfusion. Activated AMPK also stimulates other molecular signaling pathways, including endothelial nitric oxide synthetase and the p38 mitogen-activated protein kinase, which appear to have a role in preconditioning. Thus, activation of AMPK before ischemia has a number of downstream actions that may serve to protect the heart against subsequent myocardial injury.
severe nutrient starvation. However, cardiomyocyte autophagy has also been described in the hibernating myocardium and may play a role in maintaining cellular viability in ischemic cardiomyopathy. Activated AMPK is involved in the induction of autophagy. Thus, AMPK activation has diverse effects on organelles, which might affect both short-term and long-term cardiomyocyte survival in the setting of myocardial ischemia.

**Pharmacological Activators of AMPK**

The possibility that the AMPK pathway might be a target in the treatment of diabetes, cancer, and cardiovascular disease has created a great deal of interest in compounds that activate AMPK. For many years, the agent that was used for investigative purposes was the compound 5-aminomimidazole-4-carboxamide-1-b-4-ribofuranoside, more commonly referred to as AICAR. AICAR is phosphorylated in the cell and mimics the effect of AMP to activate cardiac AMPK. However, AICAR also prevents the reuptake of adenosine after release from the ischemic heart and thereby augments activation of membrane adenosine receptors. AICAR was patented as Acadesine and underwent clinical trials during coronary bypass surgery. It proved to have benefit to prevent myocardial infarction, the need for left ventricular assist device support, and early death. However, the fact that AICAR activates AMPK was not appreciated at that time, and it remains unclear whether the doses used in previous clinical trials effectively activated AMPK in the human heart.

There is now a great deal of effort in the development of specific AMPK activators. Such agents are currently the focus of several drug discovery programs, most of which are targeted at the treatment of type 2 diabetes. The first prototype drugs are now emerging, and their effects on the heart will be of substantial interest.

**Cardiomyopathy Associated With Mutations in the AMPK γ2 Gene**

Given the numerous physiological actions of activated AMPK, it is not surprising that mutations that disrupt the normal regulation of the AMPK complex are associated with abnormalities in the heart. There are 10 distinct human mutations that have been identified in the PRKAG2 gene, which encodes the AMPK γ2 subunit protein. As mentioned previously, the γ subunits contain the critical AMP-binding sites that modulate AMPK complex activity. Patients with PRKAG2 mutations demonstrate left ventricular hypertrophy, Wolff-Parkinson-White syndrome, arrhythmias, conduction system disease, and heart failure. Affected individuals demonstrate cardiomyocyte glycogen overload, which is thought to have a primary role in the pathogenesis of disease. Interestingly, the clinical manifestations associated with the PRKAG2 mutation are reminiscent of classic glycogen storage disorders, such as Danon and Pompe diseases.

The clinical manifestations depend somewhat on the specific mutation but also vary within families with the same mutation. Most patients demonstrate left ventricular hypertrophy and/or Wolff-Parkinson-White syndrome. Pathologically, these individuals have increased left ventricular wall thickness with substantial glycogen overload but not the typical myofibrillar disarray and hypertrophy associated with classic hypertrophic cardiomyopathy. Left ventricular hypertrophy can develop during childhood and is sometimes associated with ventricular outflow track obstruction, cavity dilation, and heart failure. Wolff-Parkinson-White syndrome is also commonly associated with PRKAG2 mutations. Ventricular preexcitation results from bands of glycogen-loaded cardiomyocytes that function as electric bypass tracks connecting the atria and ventricles. Excess glycogen is thought to inhibit the process of apoptosis that normally eliminates these cardiomyocytes during the development of the annulus fibrosis. Persistence of these cardiomyocyte bands can produce single or sometimes multiple functional bypass tracks in patients with PRKAG2 mutations.

The reason for glycogen overload in these hearts has been elucidated through the recent study of transgenic mice expressing PRKAG2 mutations. Perhaps the best understood is the N488I mutation, which results in the substitution of an isoleucine for the normal asparagine at the 488th position in the AMPK γ2 protein. This mutation leads to abnormally high baseline AMPK activity, which is directly linked to the development of glycogen overload, cardiac hypertrophy, and ventricular preexcitation. Excess glycogen results from accelerated glycogen synthesis rather than the impaired breakdown that is characteristic of classic glycogen storage diseases. As already discussed, activated AMPK increases cellular glucose uptake. It also increases fatty acid oxidation, which blocks glucose oxidation and thus increases the amount of intracellular glucose that is available to synthesize glycogen. Thus, cardiac glycogen overload associated with the PRKAG2 mutations appears to be due to a remodeling of glucose metabolism that enhances glucose uptake and preferentially shunts glucose into glycogen.

**Future Clinical Directions**

The actions of activated AMPK previously described have generated many questions regarding its potential role in cardiovascular disease. There is considerable interest in whether AMPK activation might indeed protect the heart against myocardial injury. To the extent that activated AMPK effectively precondition the heart, novel pharmacological approaches to AMPK activation could prove useful before high-risk revascularization procedures. Additional applications might include protecting donor hearts before transplantation and treating patients with acute ischemic syndromes who do not have access to immediate revascularization.

The role of AMPK in cardiovascular disease is not limited to the ischemic myocardium. AMPK may prove to have an important role in the vasculature. Activated AMPK affects endothelial metabolism and function, vascular smooth muscle proliferation, and angiogenesis. Like rapamycin, activated AMPK inhibits the mTOR pathway and could potentially have a role in preventing restenosis after coronary intervention. It is intriguing to consider whether the AMPK pathway could be modulated as a means of preventing atherosclerosis, restenosis, or transplant vasculopathy.
AMPK also has important metabolic effects outside of the heart that might be useful in the treatment of type 2 diabetes. Activated AMPK stimulates skeletal muscle glucose uptake and suppresses the release of glucose from the liver. Activated AMPK also improves insulin receptor signaling. It is of interest to note that both metformin and thiazolidinediones stimulate AMPK activity. Because diabetic and insulin-resistant patients are highly prone to cardiovascular disease, the potential that AMPK-directed therapy might have simultaneous metabolic, cardiac, and vascular effects would be of obvious clinical interest.

When clinical applications are considered, targeting a major conductor of the stress signaling orchestra, rather than a single player, has enormous potential to direct a wide-reaching biological response. However, despite substantial enthusiasm for examining AMPK as a therapeutic target, there are concerns that such a strategy is inherently more complex than one focused on a single player. For instance, it is possible that some orchestral players might indeed be out of tune with the desired therapeutic response. Thus, preclinical research is essential to evaluate the effects of AMPK activators in clinically relevant models of disease.

It seems likely that the application of AMPK activators to the heart would be limited to short-term use. However, if strategies are developed for the long-term use of AMPK activators for other diseases, particular attention will need to be given to evaluate whether they cause glycogen accumulation in the adult heart. AMPK activation also has an antisi-tuety action in the hypothalamus, which might cause unwanted weight gain; to the extent that this occurs, drugs would need to be designed with chemical structures that would avoid entry into the central nervous system.

Over the last decade, there have been major advances in understanding the AMPK pathway, which provide a rationale for further research to explore the potential for AMPK-directed therapy for important problems in clinical medicine. As drugs are developed that effectively modulate this pathway, clinicians practicing cardiovascular medicine are likely to hear more about this conductor of the cardiac stress response orchestra.

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