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AMP-activated Protein Kinase (AMPK): Does This Master Regulator of Cellular Energy State Distinguish Insulin Sensitive from Insulin Resistant Obesity?

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Abstract

Although a correlation exists between obesity and insulin resistance, roughly 25 % of obese individuals are insulin sensitive. AMP-activated protein kinase (AMPK) is a cellular energy sensor that among its many actions, integrates diverse physiological signals to restore energy balance. In addition, in many situations it also increases insulin sensitivity. In this context, AMPK activity is decreased in very obese individuals undergoing bariatric surgery who are insulin resistant compared to equally obese patients who are insulin sensitive. In this review, we will both explore what distinguishes these individuals, and evaluate the evidence that diminished AMPK is associated with insulin resistance and metabolic syndrome-associated disorders in other circumstances.

Keywords

Obesity; AMPK; Insulin resistant; Bariatric surgery; Fetuin-A; Insulin sensitive

Introduction

The ‘obesity epidemic’ is thought to be responsible for the rising prevalence of metabolic syndrome-associated diseases including type 2 diabetes, cardiovascular and nonalcoholic fatty liver disease (NAFLD), and certain forms of cancer [1–3]. Although the relationship between obesity and insulin resistance is a hallmark of the metabolic syndrome, it has been long recognized that some obese individuals (~25 %) are insulin sensitive [4•, 5]. In general, they have less abdominal fat (both visceral and subcutaneous) than their insulin resistant counterparts [4•, 5, 6]. In addition, they are less likely to develop atherosclerotic

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Compliance with Ethics Guidelines

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cardiovascular disease [7••], and presumably other obesity-associated comorbidities although the latter remain to be proven [8].

AMP-activated protein kinase (AMPK) is a conserved eukaryotic protein serine/threonine kinase that senses the energy status of the cell and coordinates a global metabolic response to restore energy homeostasis [9, 10]. It can also be activated by agents that increase intracellular Ca^{2+} [11, 12]. AMPK appears to be an attractive therapeutic target for metabolic syndrome-associated diseases. For example, popular anti-diabetic drugs such as metformin [13] and thiazolidinediones (TZDs) [14], the endogenous insulin sensitizing adipokine adiponectin [15], and exercise [16] all have been shown both to activate AMPK and be therapeutic for metabolic syndrome-associated diseases. Conversely, decreases in AMPK activity have been associated with an increase in such disorders in experimental animals and more recently, in humans. Table 1 provides a list of physiological and pharmacological regulators of AMPK; and Fig. 1 indicates some of the metabolic and other biological actions of AMPK in mammalian tissues.

In this review, we will describe how AMPK becomes dysregulated in obesity, and why such dysregulation is associated with insulin resistance and metabolic syndrome-associated disorders. We will focus predominantly on how these events take place in adipose tissue and liver. In addition, we will discuss the relationship of the pro-inflammatory molecule fetuin-A to insulin resistance, and the involvement of AMPK in fetuin-A regulation. Since data from humans are limited and causality is often difficult to establish, we will refer to rodent studies where applicable.

AMPK: A Multifaceted Molecule with Actions Beyond Energy Balance

An increasing body of work indicates that AMPK is a central regulator of a host of events including inflammation, oxidative/ER stress, autophagy, mitochondrial function and fatty acid oxidation, all of which when dysregulated, could be pathogenic for insulin resistance and ultimately, metabolic syndrome-associated diseases (Fig. 1). Furthermore, it has been shown that AMPK has a prominent role in the central nervous system as well as peripheral tissues. For example, leptin released by adipose tissue decreases both AMPK activity in the hypothalamus and secondarily food intake [17, 18], whereas ghrelin increases both hypothalamic AMPK and food intake [19].

Excess nutrients can down-regulate AMPK activity in peripheral tissues. For example, glucose infused at a high rate in vivo has been shown to diminish AMPK activity and cause insulin resistance in rat muscle and liver [20]; and a high level of glucose or leucine has similar effects on incubated rat muscle [21]. Similarly, rodents with diet- or genetic-induced obesity have unequivocally shown a diminished AMPK activity and insulin resistance in multiple tissues, as well as a predilection to metabolic syndrome-associated diseases [22]. As already noted, studies of human subjects also have revealed a correlation between low AMPK activity in adipose tissue and metabolic disorders associated with insulin resistance and obesity [23••, 24, 25]. However, efforts to find such a correlation in human skeletal muscle have yielded mixed results [16].

AMPK and Adipose Tissue

Rodents and in Vitro Studies

Multiple lines of evidence suggest a link between dysregulation of AMPK activity and oxidative stress, inflammation, and insulin resistance in adipose tissue. They also suggest that exercise (which increases insulin sensitivity) activates AMPK [26]. Conversely, AMPK activity has been reported to be less in the adipose tissue of obese and insulin resistant rodent models [27, 28]. In cultured 3 T3-L1 adipocytes, Gauthier et al. showed that inhibiting AMPK during lipolysis is associated with elevated oxidative stress [29]. The antagonizing effect of AMPK on oxidative stress also has been reported in other tissues [30•, 31]. As for inflammation, genetic deletion of either the α1 or β subunit of AMPK leads to adipose tissue inflammation, insulin resistance, and increased obesity in mice fed a high fat diet [32].

Humans

Decreased AMPK activity attributable to metabolic and hormonal abnormalities in humans was first reported by Kola et al. [24] in visceral adipose tissue of patients with Cushing's syndrome, a disorder marked by abnormally high plasma cortisol levels [24]. Individuals with Cushing's syndrome typically present with metabolic abnormalities including insulin resistance and a predisposition to type 2 diabetes, hypertension, and premature coronary artery disease [33]. In a separate study, the same group found that infusion of glucocorticoids into rats led to decreased AMPK activity in adipose and several other tissues [34]. Interestingly, glucocorticoids also have been demonstrated to increase oxidative stress in cultured cells [35].

More recently, studies in severely obese patients undergoing bariatric surgery have revealed an association between diminished AMPK activity, increased visceral adiposity and oxidative stress, and inflammation in multiple adipose tissue depots of insulin resistant individuals compare to a BMI-matched insulin sensitive group [23••, 25]. It is unclear from existing data whether AMPK dysregulation, oxidative stress, or inflammation occurs first. ER stress was not investigated in these studies; however, it should be emphasized that it can down-regulate AMPK activity and also affect both oxidative stress and inflammation [22]. Gregor et al. have reported that ER stress is reduced in adipose and liver of morbidly obese subjects following gastric bypass surgery [36], although they did not divide the study subjects into insulin sensitive and resistant groups. Evaluating fat biopsies post-operatively would be of great interest since it would allow investigators to determine temporally when such pathogenic factors as decreased AMPK activity, oxidative (and ER) stress and inflammation are corrected by the weight loss surgery. In addition, although bariatric surgery is generally associated with a durable remission of type 2 diabetes, about one third of severely obese diabetic patients experience a relapse within 5 years [37, 38]. Such measurements in post-operative biopsies of adipose tissue and in plasma might provide insights why such remissions and relapses occur; and what might be done to prevent the latter. For instance, if evidence of decreased AMPK activity is found, could AMPK-based therapy (i.e., metformin, TZDs, GLP-1 analogs) be useful for patients in relapse? It will also be of interest to follow non-obese offspring of these severely obese individuals to search for

early manifestation of the metabolic syndrome (such as insulin resistance, hypertriglycemia [39]) and genetic or other abnormalities in their adipose tissue. Presumably diet and exercise would warrant a trial in such individuals.

AMPK and Insulin Resistance in Liver

Similar to adipose tissue, the α1 subunit is the predominant AMPK isoform in human liver [40], and it is activated by many of the same mechanisms, including exercise [26, 41], starvation [42], IL-6 [43], and adiponectin [44]. Also it is diminished by obesity and nutrient excess [20, 45–47]. In liver, AMPK coordinates fatty acid metabolism [42] by reciprocally regulating triglyceride (TG) synthesis and fatty acid oxidation [48]. The absence or a marked decrease in AMPK activity results in increased hepatic gluconeogenesis, steatosis, and oxidative stress, as well as reductions in mitochondrial biogenesis and fatty acid oxidation [40]. Importantly, hepatic mitochondrial dysfunction (perhaps caused by reduced levels of AMPK) may precede and contribute to insulin resistance and hepatic steatosis, leading to NAFLD [49]. In contrast, activation of AMPK through a variety of means has been shown to restore normoglycemia [50, 51], and lower hepatic glucose production [50–52] and plasma TG levels in both animal models of obesity [53, 54] and type 2 diabetic patients [55]. It remains to be determined whether AMPK activity in liver differs between insulin sensitive and resistant humans. However, based on studies in rodents [50, 56, 57], AMPK activity positively correlates with insulin sensitivity.

Fetuin-A and Insulin Resistance

Similar to adipokine secretion from visceral adipose tissue, the liver can produce hepatokines. The most well-studied pro-inflammatory hepatokine is fetuin-A, a glycoprotein produced primarily by hepatocytes [58], and as reported recently, also by adipocytes [59]. Obese rodents demonstrate elevated fetuin-A mRNA and protein in liver [60–62] and serum [63, 64]. Likewise, elevated fetuin-A levels have been observed in humans with NAFLD and NASH [62, 65, 66]. Mechanistically, fetuin-A is thought to act as an inhibitor of insulin receptor signaling [67], and mice lacking fetuin-A are protected against the development of insulin resistance [68]. Both hyperglycemia [69] and the saturated fatty acid palmitate [63] stimulate fetuin-A production and secretion by hepatocytes (Fig. 2). Excess concentrations of fetuin-A in turn promote inflammatory cytokine production in at least adipose tissue and monocytes [63, 70, 71•] apparently by acting as an endogenous ligand for toll-like receptor 4 (TLR4) that allows palmitate to trigger inflammation and insulin resistance [71•] (Fig. 2). Work from our group has shown that fetuin-A also can induce inflammation in cultured endothelial cells by a similar mechanism and that AMPK can prevent this (R. Valentine et al., unpublished observations).

Clinical data have linked fetuin-A to obesity, insulin resistance [62, 72, 73], and an increased risk of developing type 2 diabetes [74–76]. In addition, fetuin-A levels have been correlated with cardiovascular disease (CVD) although only in older adults [77–79]. More specifically, it has been associated with carotid artery intima-media thickness and stiffness [80–82], endothelial dysfunction [83], and a risk of myocardial infarction and stroke [84–

86]. Interestingly, the link between fetuin-A and CVD appears to be most evident in patients with established type 2 diabetes [79, 87, 88].

AMPK Inhibits Fetuin-A

Currently, clinical trials to lower hepatic and circulating fetuin-A are limited. Weight loss produced by both bariatric surgery [89] and caloric restriction [60, 90] diminishes serum fetuin-A levels, as does short-term exercise independent of weight loss [91]. Likewise, physically active men exhibit lower serum fetuin-A levels than their inactive counterparts [92]. Similar findings have been observed using treatment with metformin [93] or rosiglitazone [94] in small human studies. Interestingly, all of these treatments can activate AMPK. As already noted, our own work has shown that AMPK can inhibit fetuin-A-induced pro-inflammatory responses in cultured endothelial cells (R. Valentine et al., unpublished data). In summary, accumulating evidence indicate that treatments that activate AMPK, including metformin, caloric restriction, curcumin, adiponectin, and salicylate, diminish fetuin-A in cultured cells and in vivo [61, 64, 93].

The novel relationship between AMPK and fetuin-A provides an intriguing framework by which AMPK may be involved in the prevention/treatment of a host of inflammatory diseases/conditions, including diabetes, metabolic syndrome and fatty liver disease. Very recently, work by Chatterjee et al. [59] revealed an adipocyte source of fetuin-A that can initiate macrophage migration and polarization in the adipose tissue in the setting of obesity. It would be interesting to investigate whether AMPK can diminish fetuin-A generation and action in adipose tissue and whether this in turn helps prevent the adipose tissue inflammation associated with obesity.

AMPK and the Microbiome

The gut microbiota affects host energy expenditure and metabolic function [95], and an altered gut microbiota has been associated with several diseases including obesity and diabetes [96]. Studies in germ-free mice by Backhed et al. revealed that the gut microbiota enhances adiposity mainly by increasing energy extraction from food and by regulating fat storage [97]. The same group subsequently demonstrated that germ-free mice are protected from diet-induced obesity in part due to an increased rate of fatty acid oxidation as a result of increases in AMPK activity in their liver and skeletal muscle [98]. More recently, a study in *Caenorhabditis elegans* showed that an alteration of microbial metabolism caused by the antidiabetic drug metformin can also have a positive effect on the host's health [99], suggesting a possible relationship between AMPK and microbial metabolism. Whether AMPK is a key target that modulates the gut microbiota remains to be elucidated. Equally unknown is whether the composition of the gut microbiome differs between insulin sensitive and resistant populations.

The Sirtuins

To date, seven sirtuins have been identified in mammalian cells. Of these, the most studied is SIRT1, a NAD^+-dependent protein deacetylase. Like AMPK, SIRT1 plays a pivotal role in mediating a wide variety of events including fuel metabolism, mitochondrial function,

senescence, the growth of cancer cells, and possibly longevity. SIRT1 expression and activity are controlled by a regulatory network that functions at several levels including transcriptional, post-transcriptional and post-translational [100]. In addition, an increased NAD^+ bioavailability has been shown to be a major regulator of SIRT1 activity [101]. A substantial body of work suggests that SIRT1, like AMPK, is activated by caloric restriction and an increase in energy expenditure [102, 103], and is down-regulated by energy oversupply [104]. Beyond this, SIRT1 has been shown to activate and be activated by AMPK [105, 106], and the two molecules share many downstream targets including but not limited to PGC1α, FOXO1, p65/NFκB [107•] (Fig. 3). For instance, AMPK and SIRT1 jointly act on the master regulator of mitochondrial biogenesis PGC-1α to enhance the synthesis of many mitochondrial proteins [107•]. Evidence that the mitochondrial SIRT3 may interact with AMPK and PGC1α in a similar fashion has been proposed very recently [108].

In the setting of metabolic syndrome, downregulation of SIRT1 in adipose tissue has been shown to increase obesity and macrophage accumulation/inflammation in rodents [109, 110]. Likewise, decreased SIRT1 expression has been observed by several investigators in adipose tissue of obese humans who are insulin resistant [111]. In our own studies, we found decreased SIRT3 and Nampt (a key enzyme involved in the NAD^+ biosynthesis) expression in the adipose tissue of insulin resistant obese individuals compared to their insulin sensitive counterpart, although we did not find a decrease in SIRT1 (Xu et al., unpublished data). Finally, in a rodent model with diet-induced obesity and insulin resistance, decreases in AMPK and SIRT1 were observed in liver (compared to control mice) and both of these parameters returned to control level after gastric bypass surgery [112]. Not surprisingly, just like AMPK, SIRT1 is viewed as an extremely attractive target to improve oxidative metabolism and mitochondrial function, and the possibility of jointly using an agent or agents that activate both molecules for treating metabolic syndrome-associated disorders has been entertained [107•]. In this context, it is noteworthy that resveratrol, a pharmacological agent at low concentration activates cellular SIRT1 while at a high dose stimulates AMPK activity in a SIRT1-independent manner in rodents [113].

Conclusion

Since the initial discovery of the role of AMPK in restoring cellular energy balance, there has been an exponential increase in the number of studies examining its effects on various physiological and pathophysiological events. It is now clear that not all obesity is the same, and that at least in white adipose tissue, a lower AMPK activity can distinguish insulin resistant from insulin sensitive obese populations. In light of the ongoing epidemic of obesity and metabolic syndrome-associated diseases, evaluating AMPK for the prevention and therapy of these disorders is certainly worthy of further exploration.

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•• Of major importance

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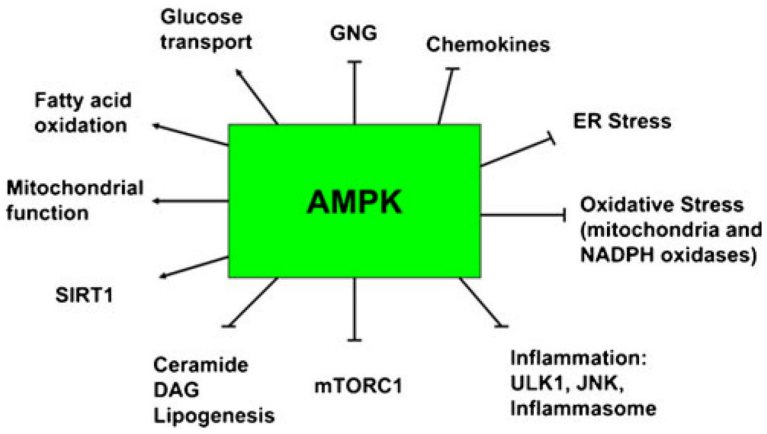

Fig. 1.

Effects of AMPK activation. In addition to the items listed in the figure, AMPK has been shown to increase eNOS, angiogenesis, autophagy, and the synthesis of anti-inflammatory cytokines such as IL-10. Furthermore, it phosphorylates the FOX Os and almost certainly many other regulatory molecules. Where studied, SIRT1 can produce many of the same effects as AMPK by activating transcriptional activators and co-activators and very likely by other mechanisms. GNG: gluconeogenesis, ULK1: UNC-51 like kinase 1, JNK: JUN activated kinase, DAG: diacylglycerol. The actions of AMPK, as listed above, have been extensively reviewed in [103–105] (Figure adapted from [22]

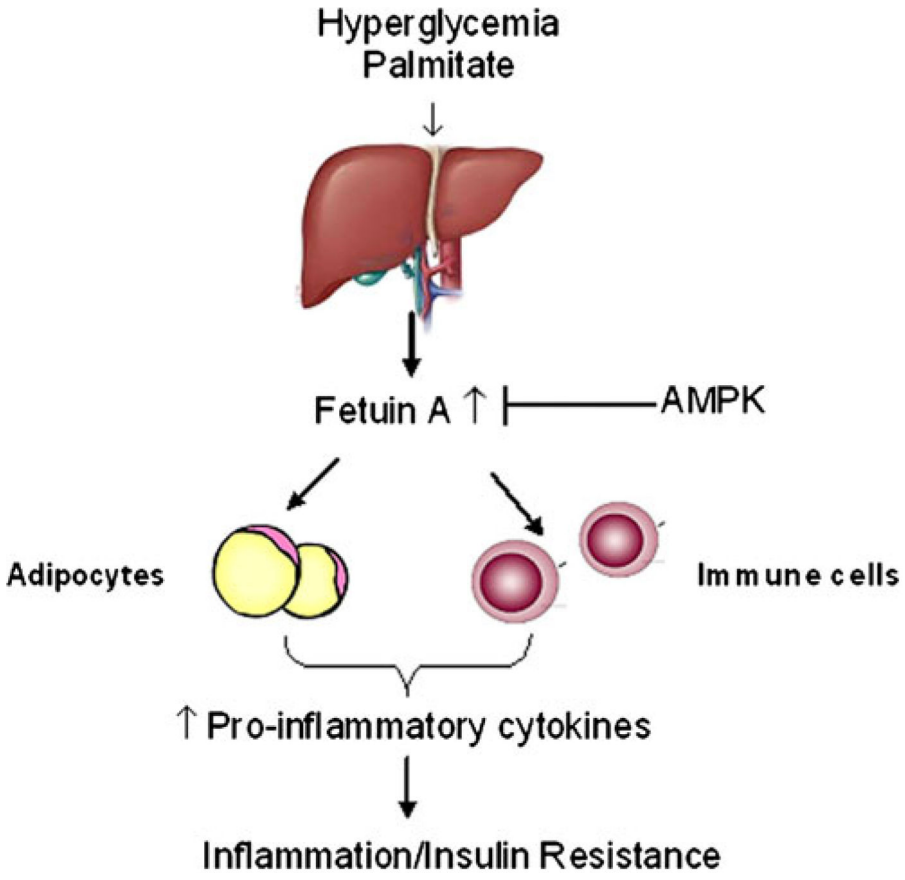

Fig. 2.

Metabolic consequences of fetuin-A production. Hepatic production of the hepatokine fetuin-A can be induced by both increased glucose and palmitate. Fetuin-A is released into the circulation and inhibits insulin signaling by binding to the insulin receptor in insulin-responsive tissues, thereby inhibiting tyrosine autophosphorylation and inducing insulin resistance. Fetuin-A also serves as an adaptor protein for saturated fatty acids, allowing them to activate Toll-like receptor 4 (TLR4) and consequently induce inflammatory signaling and insulin resistance. AMPK can act to 1) suppress fetuin-A production and secretion; 2) diminish fetuin-A induced inflammation; and 3) restore insulin signaling inhibited by fetuin-A

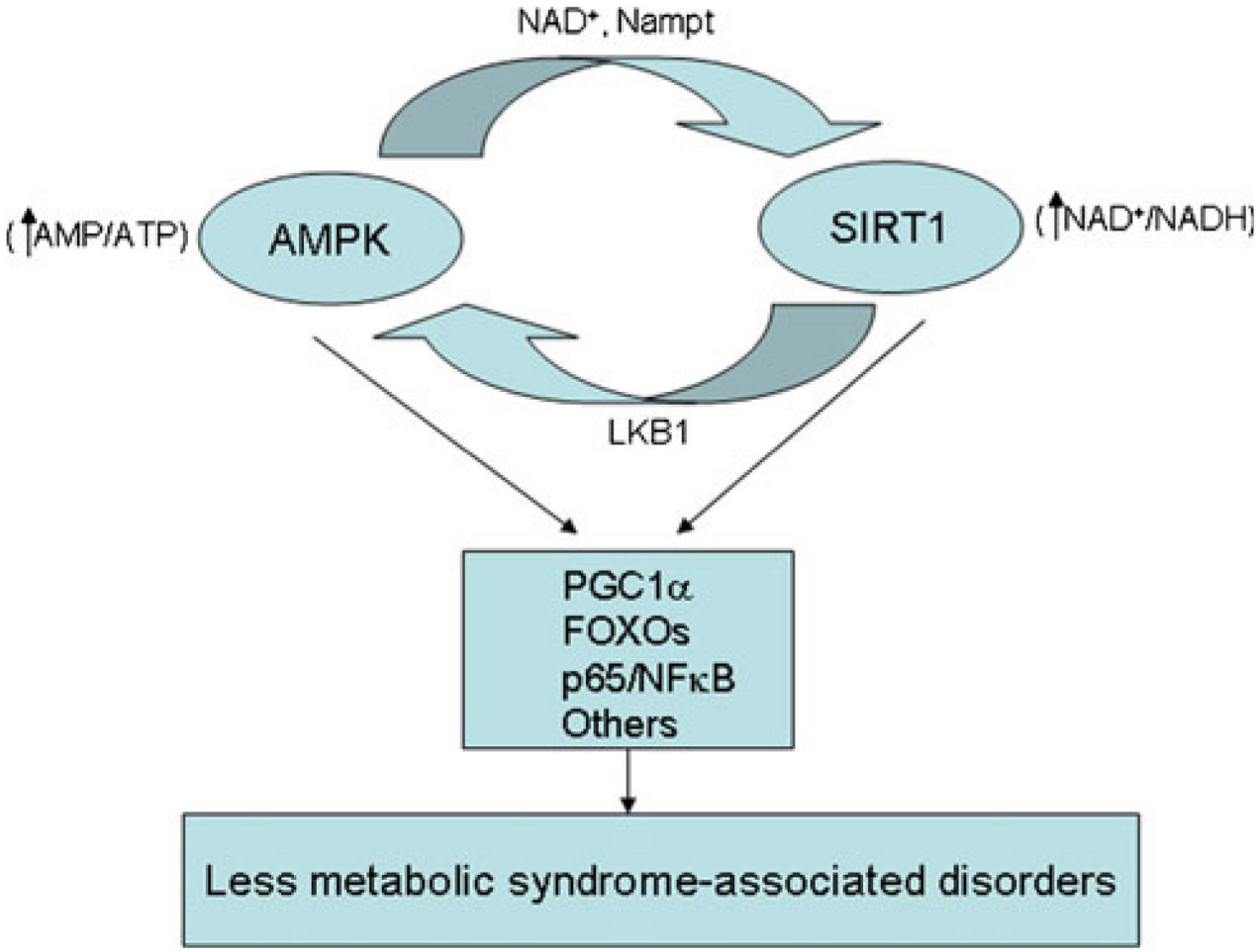

Fig. 3.

The putative AMPK/SIRT1 cycle. Activation of AMPK by means such as decreased energy state leads to activation of SIRT1 (via increasing NAD^+ and/or activity of Nampt). SIRT1 then deacetylates and activates LKB1, which in turn activates AMPK. Conversely, these events could be initiated by factors that act on SIRT1. The joint activation of AMPK and SIRT1 concurrently phosphorylate and deacetylate the listed target molecules and possibly others. The predicted result would be a decreased susceptibility to metabolic syndrome-associated disorders

Table 1

Physiologic and pharmacologic regulators of AMPK activity

Physiological activators	Physiological inhibitors	Pharmacological activators
Exercise	High glucose	Biguanides (metformin)
Caloric restriction	Branch-chain amino acids	Thiazolidinediones (TZDs)
SIRT1	Insulin	Salicylates
Adiponectin	TNF-α	Statins
GLP-1	Microbiota	Fenofibrate
Leptin	Protein phosphatases	Resveratrol
IL-6	Glucocorticoids	α-Lipoic acid
IL-10	Leptin (CNS)	Berberine
Estrogen	Ghrelin (periphery)	Curcumin
Catecholamines	Palmitate	
Leptin (periphery)		
Ghrelin (CNS)		

Note: This list is meant to illustrate some of the most well established regulators of AMPK. For a more exhaustive list and primary references refer to [114, 115]