AMPK, insulin resistance, and the metabolic syndrome

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Insulin resistance (IR) and hyperinsulinemia are hallmarks of the metabolic syndrome, as are central adiposity, dyslipidemia, and a predisposition to type 2 diabetes, atherosclerotic cardiovascular disease, hypertension, and certain cancers. Regular exercise and calorie restriction have long been known to increase insulin sensitivity and decrease the prevalence of these disorders. The subsequent identification of AMP-activated protein kinase (AMPK) and its activation by exercise and fuel deprivation have led to studies of the effects of AMPK on both IR and metabolic syndrome–related diseases. In this review, we evaluate this body of literature, with special emphasis on the hypothesis that dysregulation of AMPK is both a pathogenic factor for these disorders in humans and a target for their prevention and therapy.

Introduction

The fuel-sensing enzyme AMP-activated protein kinase (AMPK) was first described as an enzyme activated by changes in the AMP/ATP ratio that could both increase cellular ATP generation (e.g., fatty acid oxidation) and diminish ATP use for less critical processes (e.g., fatty acid, triglyceride, and protein synthesis) (1). In addition to glucose transport, lipid and protein synthesis, and fuel metabolism, AMPK regulates a wide array of other physiological events, including cellular growth and proliferation, mitochondrial function and biogenesis, and factors that have been linked to insulin resistance (IR), including inflammation, oxidative and ER stress, and autophagy (Figure 1A). Furthermore, AMPK does so by phosphorifying both key enzymes and transcriptional activators and coactivators.

Here, we examine 2 hypotheses suggested by more recent studies: (a) dysregulation of AMPK plays an important role in the pathogenesis of IR and metabolic syndrome–associated diseases in humans and experimental animals; and (b) strategies that activate AMPK can be harnessed for the prevention and treatment of these abnormalities. These hypotheses emanated from associations between the metabolic syndrome and some downstream targets of AMPK, such as glucose transport and lipogenesis (2–8).

In addition, exercise (9) and electrically induced contractions (10) were shown to activate AMPK. These observations, coupled with epidemiological evidence that diseases associated with the metabolic syndrome (e.g., type 2 diabetes, hypertension, atherosclerotic cardiovascular disease [ASCVD], and even certain cancers) are less prevalent in physically active people (11–13) and the demonstration that regular exercise improves whole-body insulin action (11, 12), suggest a central role for AMPK in regulating insulin sensitivity. Such studies also raise the possibility that pharmacological AMPK activators as well as exercise could be used for ameliorating IR in type 2 diabetes (4, 8).

In model systems, sustained decreases in AMPK activity accompany IR, whereas AMPK activation increases insulin sensitivity (5, 6, 13). In addition, decreases in AMPK activity accompanying IR were described in adipose tissue of humans with Cushing's syndrome, an effect attributable to high levels of glucocorticoids (14), and in a subgroup of very obese patients undergoing bariatric surgery who were insulin resistant (15, 16). The latter comprise approximately 75% of bariatric surgery patients and show a greater predisposition to metabolic syndrome–associated diseases than the remaining 25% of such patients who are equally obese, but less hyperinsulinemic and more insulin sensitive (17–19).

Insulin resistance in physiology and disease

Studies with a perfused rat hindquarter preparation demonstrated that insulin-stimulated glucose uptake in skeletal muscle is reduced in fed versus fasted rats (20) and in sedentary versus recently exercised rats (21), suggesting that the fed and sedentary rats are essentially more insulin resistant. Such IR is physiological, rather than disease associated, and dynamically responds to changes in nutritional and physical activity.

In contrast, in patients with the metabolic syndrome, IR and hyperinsulinemia are sustained and are associated with impaired insulin action and a predisposition to multiple diseases (Figure 1B) (22–24). Whether IR plays an active role in the pathogenesis of these diseases or defends against a “glucolipotoxic” insult that may harm insulin-sensitive tissues (e.g., by increasing oxidative stress) is presently under debate (25, 26). A diagnosis of the metabolic syndrome is based on measurements of plasma glucose (less than 100 mg/dl) and other parameters such as triglycerides, HDL cholesterol, blood pressure, and waist circumference; abnormalities in 3 of the 5 of risk factors are required for a metabolic syndrome diagnosis (24, 27). Interestingly, individuals with the metabolic syndrome typically have a decreased capacity for exercise (28) and show evidence of low-grade inflammation (29), similar to patients with obesity and type 2 diabetes (24, 29). Furthermore, oxidative and ER stress, mitochondrial dysfunction, altered lipid metabolism, and dysregulation of AMPK and a closely related group of fuel-sensing molecules, the sirtuins, have also been described in both humans and experimental animals with metabolic syndrome–associated diseases and appear to promote their pathogenesis (22, 24).
AMPK actions and putative linkage between decreased AMPK activity and metabolic syndrome–associated diseases. (A) Effects of AMPK activation. In addition to activating processes that produce ATP and diminish its consumption, AMPK inhibits inflammation, ER and oxidative stress, and activates autophagy, all of which appear to be involved in the pathogenesis of IR. Where studied, SIRT1 can produce many of the same effects as AMPK (see also text and Figure 3). The above-listed actions of AMPK and others have been extensively reviewed (5, 6, 67). GNG, glucose-6-phosphatase; ULK1, UNC-51–like kinase 1; JNK, JUN-activated kinase. (B) Proposed link between AMPK and IR in the setting of the metabolic syndrome. It has long been held that the combination of overnutrition (obesity), inactivity, and indeterminate genetic factors predispose humans to the metabolic syndrome and associated disorders. Based on studies of the offspring of patients with metabolic syndrome–associated disorders, hyperinsulinemia and IR may antedate such diseases as hypertension, type 2 diabetes, and ASCVD by many years (reviewed in ref. 28). Likewise, studies in both experimental animals and humans have implicated oxidative and ER stress and decreased adiponectin in the pathogenesis of these disorders. An emerging body of evidence, predominantly but not exclusively from animal models, suggests that dysregulation of AMPK, and probably sirtuins, could both contribute to these abnormalities and be a target for their prevention and therapy (13). One possibility is that such dysregulation of AMPK and sirtuins causes epigenetic changes (methylation, acetylation, etc.) that could contribute to the diseases (151). NAFLD, nonalcoholic fatty liver disease; T2D, type 2 diabetes. Effects of exercise

As already noted, exercise increases whole-body insulin sensitivity and diminishes plasma insulin levels in humans. In addition, both epidemiological and randomized, prospective studies showed that regular exercise diminishes the likelihood that humans will develop ASCVD (35, 36) and type 2 diabetes (28, 37–39). Thus, the benefits of exercise are widely attributed to its effect on reducing whole-body IR and hyperinsulinemia. Although this explanation, which assumes a systemic effect of exercise on insulin action, still has merit, the discovery in rodents that exercise acutely increases AMPK activity in adipose tissue (40) and aortic endothelium and media (41, 42), as well as liver (40) and muscle, raises the possibility that AMPK activation in specific and underappreciated tissues contributes to its beneficial effects. For instance, in rodent aorta, treadmill running increases the activity or expression of 3 known AMPK regulators, LKB1, CAMKKβ, and SIRT1, and it concurrently activates endothelial nitric oxide synthase (eNOS) (41), an enzyme generally thought to protect against atherogenesis in experimental animals (43).

AMPK activators – pharmacological and hormonal

Metformin. In 2001, metformin, a widely used antidiabetic drug that modestly increases insulin sensitivity, was reported to act as an AMPK activator (44). An extended follow-up study (45) showed that metformin use was associated with a significant decrease in the incidence of myocardial infarction and a 36% decrease in all-cause mortality. Furthermore, multiple studies have suggested that the incidence of many cancers is diminished in diabetic patients treated with metformin (46), although this conclusion has been questioned (47). Metformin does not act directly on LKB1 or AMPK, but rather appears to activate AMPK by modestly
inhibiting complex I of the mitochondrial electron transport chain and thus decreasing the cellular energy state (48). In liver, this decreased energy state is sufficient to diminish glucose production, even in mice lacking hepatic AMPK, indicating AMPK-independent effects of metformin. Moreover, metformin-induced accumulation of AMP, which inhibits adenylate cyclase and reduces cAMP levels and PKA activity, may be an AMPK-independent mechanism by which metformin antagonizes glucagon signaling (49). Metformin has been shown to activate AMPK in many tissues, including adipose, skeletal muscle, and heart, although, to date, evidence that genetic downregulation of AMPK prevents its biological actions has been obtained only in cultured cells.

Adiponectin. AMPK is also activated by the adipokine adiponectin (50, 51). Notably, diminished serum adiponectin levels are associated with IR and appear to be a strong predictor of type 2 diabetes and cardiovascular disease in obese humans (52–54). Conversely, elevated adiponectin levels are associated with increased insulin sensitivity, a lower incidence of type 2 diabetes that is independent of obesity, and a decreased risk of coronary heart disease (52–54). Adiponectin also lowers incidence of type 2 diabetes that is independent of obesity, and adiponectin levels are associated with increased insulin sensitivity, a mechanism that protects against dephosphorylation, maintaining the kinase in an active form by dephosphorylation catalyzed by the action of protein phosphatases (PPases). Binding of ADP and AMP to the γ subunit of AMPK protects against dephosphorylation, maintaining the kinase in an active conformation, although recent studies suggest that ADP is likely to be the important physiological regulator of this process. ADP and AMP have also been reported to promote LKB1-mediated phosphorylation of AMPK, whereas calcium directly activates CaMKKβ. In addition, AMP causes a modest allosteric activation of AMPK. Finally, glycogen (and branched-chain carbohydrates) bind to the glycogen-binding domain within the β subunit, allosterically inhibiting AMPK. P, phosphorylation of T172.

Studies in genetically obese and fat-fed rodents
Decreased AMPK activity occurs in many genetic rodent models with a metabolic syndrome phenotype, including ob/ob mice (leptin deficient), fa/fa rats (leptin receptor deficient) and the male ZDF rat (leptin receptor deficient with a mutation in the leptin receptor (13). In all of these rodents, therapy with the AMPK activator AICAR (5-aminoimidazole-4-carboxamide-1-beta-d-ribofuranoside) improved IR and glucose homeostasis (70–73).

Studies in rodents genetically deficient in whole-body, liver, and skeletal muscle AMPK
The picture that emerges from studies in rodents deficient in AMPK activity and fed a high-fat diet to produce IR is less clear. Transgenic overexpression of an inactive α2 subunit (α2i TG) and AMPK knockout models have been generated that would reduce or eliminate AMPK activity in muscle (α2, β1/β2, γ3), liver (β1), or...
the whole body (α2 or α1). In general, in rodents challenged with a high-fat diet, the effects have been equivocal, with some demonstrating that elimination of AMPK in muscle or liver plays little role in generating or exacerbating IR (reviewed in ref. 79), whereas others clearly show an increase in IR compared with control rodents (80, 81). Until the reasons for the differing results are resolved, the question of whether a decrease in AMPK activity predisposes to IR and the metabolic syndrome will remain controversial.

From a treatment perspective, an intriguing set of observations has recently been made by 2 groups regarding the necessity of AMPK. Um and colleagues (82) demonstrated that resveratrol, a polyphenol found in red wine and a known AMPK activator (78), prevents IR in wild-type mice placed on a high-fat diet, but not in whole-body AMPK α2 knockout mice. Likewise, under very similar conditions, Jelenik et al. (83) found that hepatic IR is no longer alleviated by dietary n-3 polyunsaturated fatty acid supplementation when AMPKα2 is not present. Whether other compounds or dietary supplements require the presence of AMPK for their anti-IR properties remains to be determined.

The AMPK-SIRT1 cycle
Sirtuins are a group of histone/protein deacetylases that are regulated by changes in the cellular redox state (NAD+/NADH ratio) and increases in nicotinamide phosphoribosyltransferase (NAMPT), the rate-limiting enzyme for NAD synthesis. Sirtuins have been evaluated extensively because of their apparent role in combating aging (84, 85). SIRT1, the most studied member of this family, responds to overfeeding, starvation, changes in energy expenditure and exercise (13), as well as to adiponectin (54), much as AMPK does, although with somewhat different timing (13). SIRT1 can activate AMPK by deacetylating the upstream kinase LKB1, which promotes LKB1 translocation from the nucleus to the cytosol, where it is activated and in turn phosphorylates and activates AMPK (86–88). Likewise, AMPK can activate SIRT1 by increasing the NAD+/NADH ratio or the expression/activity of NAMPT (89). Collectively, these findings suggest the existence of an AMPK-SIRT1 cycle that links the cell’s energy and redox states (13). In addition, AMPK and SIRT1 (and most likely other sirtuins) act on common transcriptional activators and coactivators, including the mitochondrial master regulator PGC1α and members of the FoxO family. Finally, both AMPK and SIRT1 activators can decrease atherosclerosis and prevent diabetes in experimental animals (13, 90).

Beneficial actions of AMPK
AMPK activation is associated with a wide array of beneficial effects on metabolic syndrome–associated diseases. Its potential benefits in pancreatic β cells, liver, and muscle have been reviewed elsewhere (6, 7, 13, 91). Here, we will focus on adipose tissue and 2 cell types that until recently have received less attention in the context of IR, macrovascular endothelium, and leukocytes.

Vascular endothelium. Early studies demonstrated that AMPK and IR are linked in the vascular endothelium (92). Human umbilical vein endothelial cells (HUVECs) incubated for 24 hours in high-glucose medium become insulin resistant and show decreased mitochondrial membrane potential, abnormalities that were prevented when AMPK was activated by various means (92–94). Subsequent studies showed that pharmacological AMPK activators and genetic AMPK overexpression could prevent inflammation (i.e., NF-κB pathway transactivation), oxidative stress, and apoptosis induced by incubation with the fatty acid palmitate or the inflammatory cytokine TNF-α (95, 96).

Another action of AMPK in endothelial cells in an elevated glucose setting is the phosphorylation of eNOS on serine 1177 (97). This modification enhances its ability to synthesize NO, a molecule that diminishes oxidative stress and possibly athrogenesis in the aorta (43). Likewise, statins have been shown to activate AMPK and increase NO synthesis in HUVECs and in whole aorta in mice (98), effects that may contribute to their antiatherosclerotic action not accounted for by cholesterol lowering (98, 99). Direct effects of AMPK on atherosclerosis have also been demonstrated in AMPK knockout models. For instance, loss of AMPKα2 in apoE-deficient mice exacerbates atherosclerosis when these mice are fed an atherogenic diet (100). Additionally, various AMPK activators (AICAR and polyphenols) have been shown to prevent atherosclerosis, with the natural polyphenol, berberine, working specifically through AMPK (101).

Macrophase activation and adipose tissue inflammation
Macrophase recruitment and activation (i.e., conversion or partial conversion of antiinflammatory M2 to proinflammatory M1 macrophages) are central features of chronic low-grade inflammatory diseases, including many associated with the metabolic syndrome. Adipose tissue of obese, insulin-resistant humans and experimental animals contain markedly increased numbers of proinflammatory macrophages, which are thought to be responsible both for removing dead adipocytes and for the inflammation that precedes IR (102–104). In addition, macrophase invasion and inflammation have been observed in the islets of humans and various rodents with both type 1 and type 2 diabetes (105).

AMPK was first implicated in macrophase regulation in studies showing that AMPK activators diminish inducible NOS (iNOS, also known as NOS3) synthesis in macrophages and adipocytes (106). Subsequently, Sag et al. (107) reported that treatment of macrophages with antiinflammatory cytokines, such as IL-10 and TGF-β, rapidly activated AMPK in these cells, whereas the proinflammatory stimulus LPS diminished AMPK activity. Likewise, inhibition of AMPK activity by RNAi or transfection of an inactive AMPK mutant enhanced LPS-induced increases in the inflammatory cytokines TNF-α and IL-6 and diminished IL-10 in these cells. More recently, Yang and coworkers (108) demonstrated that increased AMPK activity, caused by the expression of a constitutively active AMPKα1, inhibits both LPS and palmitate-induced NF-κB signaling in macrophages. They also observed that inactivating AMPK in macrophages in a macrophase/adipocyte coculture system inhibited both insulin signaling and glucose uptake in the adipocytes (i.e., it produced IR). Finally, the same investigators found that AMPK activation increased SIRT1 expression in macrophages and that this led to the deacylation and downregulation of NF-κB (i.e., decreased inflammation).

The critical nature of AMPK in macrophages was recently underscored in a study examining wild-type mice that received transplanted bone marrow from AMPKβ1–deficient mice and were then fed a high-fat diet (109). As a consequence of having virtually no AMPK activity in their macrophages, these mice had higher serum levels of inflammatory cytokines, more bone marrow–derived macrophase infiltration into fat pads with gene expression patterns consistent with M1-polarized cells, and increased systemic and hepatic IR.

Additional evidence of AMPK and SIRT1 links to inflammation
Why changes in AMPK and SIRT1 exert effects on inflammation and other events that alter insulin sensitivity is incompletely under-
Insulin resistance and decreased AMPK in humans

The association of decreased AMPK activity and IR has been conclusively demonstrated in the adipose tissue of both very obese individuals undergoing bariatric surgery and patients with Cushing’s syndrome.

Cushing’s syndrome. Kobonits and coworkers observed decreased AMPK activity in the visceral adipose tissue of patients with Cushing’s syndrome, most of whom had elevated plasma cortisol levels due to a functioning adrenal adenoma (14). The same investigators found that infusion of glucocorticoids into rodents also diminished AMPK activity (126). Individuals with Cushing’s syndrome are characterized by IR, increases in visceral fat, and a predisposition to both type 2 diabetes and ASCVD. Similar abnormalities are observed in patients treated with high doses of glucocorticoids for extended periods, although their effect on ASCVD is somewhat controversial (127). Interestingly, incubation of adipocytes with cortisol causes IR that is associated with increases in oxidative stress, but, as expected, not with inflammation (128).

Patients undergoing bariatric surgery. Gauthier (15) and Xu (16) and their coworkers observed that AMPK activity is significantly diminished (30%–50%) in the adipose tissue of 75% of the severely obese individuals undergoing bariatric surgery who are insulin resistant, compared with the remaining 25% who are insulin sensitive. Such decreases in AMPK activity were observed in omental, subcutaneous abdominal, and epiploic fat and were accompanied by increased oxidative stress both in these depots and in plasma (129), as had been reported previously (130). In contrast, differences in gene expression were more depot specific. In general, increases in inflammatory genes such as IFNG, angiotensinogen (16), IL1B (131), IL8, and chemokines (132), accompanied by macrophage and lymphocyte infiltration (16, 131, 133) and decreases in the expression of genes for PGC1A (16) and SIRT1 (133) and enzymes related to β oxidation of fatty acids and the citric acid cycle (134), were observed in visceral adipose tissue of insulin-resistant compared with insulin-sensitive subjects. The strongest predictors of IR in these patients were macrophage infiltration of adipose tissue, together with decreased plasma adiponectin (133).

Implications of the findings in bariatric surgery patients. An increasing body of evidence indicates that various bariatric surgery procedures reverse type 2 diabetes and other disorders associated with the metabolic syndrome, including dyslipidemia, hypertension,
and polycystic ovary disease (19, 135). In addition, bariatric surgery diminishes long-term mortality (up to 20 years after surgery) from coronary heart disease by 30% (18) and the prevalence of solid tumors by 70% (5 years after surgery) (19). Interestingly, the effect on cardiovascular disease mortality was observed primarily in patients in the 2 highest quintiles of plasma insulin preoperatively (18) (i.e., the most insulin-resistant subjects). These patients also have low AMPK activity, increased oxidative and (presumably) ER stress, and inflammation in their adipose tissue (16).

Whether the decreases in AMPK and SIRT1 or the increases in oxidative and ER stress and inflammation disappear more rapidly following bariatric surgery remains to be determined. Also requiring study is why some obese people remain insulin sensitive, whereas the majority of them are insulin resistant. In addition to the possibilities already discussed, such factors as alterations in capillary density and permeability (136, 137), differences in collagen VI deposition (53, 138, 139), the release of LPS from bacteria by the gut microbiome (140–142), alterations of lipid droplet proteins such as FSP27 (CIDEc) that regulate the rates of lipid deposition and lipolysis in adipose tissue (19, 143), and events that cause an imbalance between nutrient load and mitochondrial function (144), need to be considered. With respect to the microbiome, AMPK activity is significantly increased in tissues of germ-free mice (145) and in mice treated with antibiotics (146), suggesting that AMPK suppression by factors released by bacteria of the gastrointestinal tract or other sites may be a normal occurrence. Finally, ER stress has not yet been compared in the adipose tissue of insulin-sensitive and -resistant obese patients. On the other hand, like oxidative stress and inflammation, ER stress diminishes over time after bariatric surgery (147).

Other tissues. Efforts to determine whether decreased AMPK activity occurs in other tissues, most notably the skeletal muscle of humans with metabolic syndrome-associated disorders, have yielded mixed results. One group reported decreased AMPK activity in the muscle of obese, insulin-resistant patients, including some with type 2 diabetes (148), and another reported decreased AMPK activation by exercise in obese and diabetic patients (149). Others have not observed such effects, however (6, 22, 150).

Concluding remarks
The findings presented in this review strongly suggest a close link between dysregulation of AMPK and IR in both rodents and humans. AMPK activity is diminished in adipose tissue of very obese insulin-resistant people, in whom it is associated with increases in oxidative stress and more variable changes in gene expression. These changes are also associated with alterations in the release of numerous humoral factors that could contribute to IR and dysfunction in other tissues that lead to metabolic syndrome-associated diseases (Figure 1B).

What is not yet clear is whether the decreases in AMPK and SIRT1 and possibly other sirtuins are primary events that promote IR and metabolic syndrome-associated disorders or if decreased AMPK and SIRT1 are components of adaptive responses to IR, oxidative and ER stresses, and inflammation. AMPK can decrease all of these factors, and these stressors in turn can diminish AMPK activity (Figure 3). Determining causality in humans may prove difficult; however, time-course studies in tissue and plasma from severely obese individuals after bariatric surgery and similar measurements in normal-weight offspring of people with metabolic syndrome–associated diseases, who often show early evidence of IR (28), might prove useful.

Another question is: why focus on AMPK when, hypothetically, oxidative and ER stress and inflammation could be therapeutic targets? A simplistic answer is that the safety and efficacy of therapies that activate AMPK are more established. Thus, AMPK can be activated by exercise and calorie restriction, whose safety and efficacy for preventing and, to some extent, treating metabolic syndrome–associated disorders such as type 2 diabetes, hypertension, and ASCVD, are reasonably established. In addition, perhaps fortuitously, pharmacological agents developed for the treatment of type 2 diabetes, such as metformin, TZDs, GLP1 agonists, and dipeptidyl peptidase IV (DPP IV) inhibitors, have all been shown to activate AMPK, and in several instances, have demonstrated utility in preventing the progression of impaired glucose tolerance to type 2 diabetes. Finally, the identification of potent and specific AMPK activators appears to be imminent. If so, we may soon be able to determine more directly the therapeutic utility of AMPK activation for the prevention and treatment of metabolic syndrome–associated disorders.

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