Review

Targeting AMP-activated protein kinase as a novel therapeutic approach for the treatment of metabolic disorders

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Abstract

In the light of recent studies in humans and rodents, AMP-activated protein kinase (AMPK), a phylogenetically conserved serine/threonine protein kinase, has been described as an integrator of regulatory signals monitoring systemic and cellular energy status. AMP-activated protein kinase (AMPK) has been proposed to function as a 'fuel gauge' to monitor cellular energy status in response to nutritional environmental variations. Recently, it has been proposed that AMPK could provide a link in metabolic defects underlying progression to the metabolic syndrome. AMPK is a heterotrimeric enzyme complex consisting of a catalytic subunit \( \alpha \) and two regulatory subunits \( \beta \) and \( \gamma \). AMPK is activated by rising AMP and falling ATP. AMP activates the system by binding to the \( \gamma \) subunit that triggers phosphorylation of the catalytic \( \alpha \) subunit by the upstream kinases LKB1 and CaMKK\( \beta \) (calmodulin-dependent protein kinase kinase). AMPK system is a regulator of energy balance that, once activated by low energy status, switches on ATP-producing catabolic pathways (such as fatty acid oxidation and glycolysis), and switches off ATP-consuming anabolic pathways (such as lipogenesis), both by short-term effect on phosphorylation of regulatory proteins and by long-term effect on gene expression. As well as acting at the level of the individual cell, the system also regulates food intake and energy expenditure at the whole body level, in particular by mediating the effects of insulin sensitizing adipokines leptin and adiponectin. AMPK is robustly activated during skeletal muscle contraction and myocardial ischaemia playing a role in glucose transport and fatty acid oxidation. In liver, activation of AMPK results in enhanced fatty acid oxidation as well as decreased glucose production. Moreover, the AMPK system is one of the probable targets for the anti-diabetic drugs biguanides and thiazolidinediones. Thus, the relationship between AMPK activation and beneficial metabolic effects provide the rationale for the development of new therapeutic strategies in metabolic disorders.

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Résumé

L’AMPK, une nouvelle cible thérapeutique pour le traitement des maladies métaboliques

De nombreuses études réalisées chez l’homme et les rongeurs ont récemment permis d’identifier l’AMPK (AMP-activated protein kinase) comme un senseur métabolique incontournable permettant l’ajustement précis des besoins et disponibilités énergétiques cellulaires et systémiques. Il a été suggéré que l’AMPK pourrait être impliquée dans la genèse des défauts métaboliques qui aboutissent au développement du syndrome métabolique. L’AMPK est un complexe hétérotérrérique constitué d’une sous-unité catalytique \( \alpha \) et de deux sous-unités régulatrices \( \beta \) et \( \gamma \). L’AMPK est activée par une augmentation de la concentration intracellulaire d’AMP et d’une diminution concomitante des niveaux d’ATP. La liaison de l’AMP à la sous-unité \( \gamma \) active le système en favorisant la phosphorylation de la sous-unité \( \alpha \) par les kinases LKB1 et CaMKK\( \beta \) (calmodulin-dependent protein kinase kinase). Lorsqu’elle est activée, l’AMPK contrôle la balance énergétique en augmentant les réactions métaboliques génératrices d’ATP (comme l’oxydation des acides gras et la glycolyse) et en inhibant les voies anaboliques consommatrices d’ATP (comme la lipogénèse), par des effets à court terme en régulant l’activité des enzymes impliquées dans ces voies métaboliques et à long terme en modulant l’expression de gènes. L’AMPK agit aussi bien au niveau cellulaire que systémique en relayant les effets des adiponectines, leptine et adiponecine. L’AMPK est fortement activée en réponse à la contraction musculaire et à l’ischémie cardiaque intervenant dans le contrôle du transport du

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1. Introduction

Developed and developing countries of the world face a global epidemic of related conditions, i.e. type 2 diabetes, obesity and the metabolic syndrome [1]. Although these conditions clearly have a genetic component, the rapid increase in the prevalence of these conditions in populations throughout the world suggests the contribution of environmental factors. Obesity and metabolic syndrome, additional risk factors for type 2 diabetes, arise due to an imbalance between energy intake (consumption of processed foods with high energy and low fibre content) and energy expenditure (reduction in physical exercise due to sedentary lifestyle). Non-pharmacological approaches including diet modification, regular exercise and patient education form the cornerstones of therapy [2]. When lifestyle modification fails to achieve or sustain adequate glycaemic control, oral antidiabetic agents (including insulin sensitizers, α-glucosidase inhibitors and β-cell secretagogues) or insulin therapy are typically used to manage the disease. Exciting recent development accumulated over the past five years has provided evidence that the "fuel gauge" AMP-activated protein kinase (AMPK) is one of the probable target of major antidiabetic drugs, biguanides and thiazolidinediones (TZDs) and of insulin sensitizing adipokines (leptin, adiponectin and resistin), thus providing support for the targeting of AMPK in drug development [3]. In the present review, we update those topics and discuss new findings that suggest that AMPK is emerging as an attractive pharmacological target for the treatment of metabolic disorders.

2. Structure and regulation of AMPK

Important progress has recently been made in the understanding of the physiological role of AMPK at both the cellular and organism level [3]. This is in part due to the development of transgenic and knockout (KO) mouse models that have made it possible to study distinct physiological functions for AMPK isoforms [4]. AMPK is a heterotrimeric complex comprising a catalytic α subunit and regulatory β and γ subunits. All three subunits are encoded by multiple genes (α1, α2, β1, β2, γ1, γ2, γ3) yielding to 12 heterotrimeric combinations, with splice variant adding to the diversity [3]. It is still unclear what cellular consequences the composition in AMPK isoform may have but this raised important questions about the function of each AMPK complex in relation with their particular subcellular localization and/or specific targets. Thus, a recent study investigated the isoform composition of AMPK complexes in human skeletal muscle and found that only 3 of the 12 theoretically possible AMPK complexes were present (α2β2γ1 >> α2βγ3 = α1β2γ1) [5]. The conventional serine/threonine kinase activity of AMPK is supported by α subunits, which contain at the N-terminal region a threonine residue (Thr172) whose phosphorylation is required for AMPK activation [3]. The C-terminal region of α subunits is required for the association with the other two subunits, β and γ (Fig. 1). The β subunits contain a C-terminal region required for the association with α and β subunits and a central region that allowed AMPK complex to bind glycogen. The γ subunits contain four tandem repeats known as cystathionine β-synthase (CBS) motif which bind two molecules of AMP or ATP in a mutually exclusive manner [3]. Binding of AMP (on γ subunit) activates AMPK allosterically and promotes phosphorylation of α subunit (on Thr 172) by upstream kinases as protein kinase LKB1 (a tumour suppressor whose germline mutations in humans are the cause of Peutz-Jeghers syndrome) or the CaMKKβ (calmodulin-dependent protein kinase kinase) [3]. AMP binding also inhibits Thr 172 dephosphorylation by protein phosphatase while binding of ATP strongly inhibits the activation of AMPK (Fig. 1).

To sustain metabolism, intracellular ATP levels must be maintained within a narrow range. This is achieved both at the cellular level as well as at the systemic level encompassing regulation of cellular catabolic and anabolic pathways. The coordination of these processes may be achieved through the activation of AMPK functioning as a "metabolic master switch" that mediates the cellular adaptation to nutritional environmental variations. AMPK is activated in response to environmental or nutritional stress factors, which deplete intracellular ATP levels including heat shock, hypoxia, glucose...
deprivation or prolonged exercise (Fig. 2). Under conditions in which cellular energy demands are increased or when fuel availability is decreased, intracellular ATP is reduced and AMP levels rise [3]. In eukaryotic cells, adenylate kinase maintains the reaction 2ADP ↔ ATP + AMP close to equilibrium making the AMP/ATP ratio a more sensitive indicator of compromised energy status than the ADP/ATP ratio. AMPK is activated as described above after an increase in AMP level, allosteric modifications and Thr 172 phosphorylation via upstream AMPK kinases [3]. It is noteworthy that each mechanism is interactive and is tightly integrated to the overall regulation of kinase activity.

3. Regulation of glucose transport and fat oxidation in skeletal muscle

Skeletal muscle is the major site of insulin-stimulated glucose disposal and insulin resistance in this tissue is one of the earliest contributing factor to the pathogenesis of type 2 diabetes. One important finding is that activation of muscular AMPK by physical activity (one of the most potent physiological AMPK activator) or by a pharmacological compound called AICAR (5-amino-imidazole-4-carboxamide ribonucleoside, metabolized to ZMP which is an analogy of AMP) increases muscle glucose uptake concomitantly with glucose transporter 4 (GLUT4) translocation to the plasma membrane [6,7]. Interestingly, AMPK-induced glucose transport occurs through a mechanism distinct from that used by the classical insulin-signalling pathway. In consequence, AMPK enhanced glucose transport in skeletal muscle is observed both in rodents or in humans even if insulin resistance is present suggesting that muscular AMPK could be a therapeutic target for the management of insulin resistant state [3]. Additive mechanism during chronic muscular AMPK activation such as increase in oxidative capacity (via mitochondrial biogenesis after increased expression of peroxisome-proliferator-activated receptor γ coactivator 1α (PGC1α) [8]), increase in expression of genes encoding GLUT4 and hexokinase II and increase in fatty acids oxidation in skeletal muscle are of particular importance. AMPK exerts control in part by regulating fatty-acid oxidation through the phosphorylation of acetyl-CoA carboxylase 2 (ACC2) and mitochondrial biogenesis through increasing the expression of proteins vital for proper mitochondrial function such as citrate synthase and succinate dehydrogenase. Reductions in AMPK-stimulated activity have recently been implicated in the reduced mitochondrial function and dysregulated intracellular lipid metabolism associated with aging-induced insulin resistance and type 2 diabetes [9]. Deposition of lipids in tissue is a hallmark defect in insulin resistant state. According to the lipotoxicity hypothesis, local accumulation of acyl-CoAs (which can originate from internal stores or circulating fatty acids), which are the precursors of diacylglycerols and ceramides, may activate a serine kinase cascade leading to defects in insulin signalling and glucose transport. Cellular lipids content is determined by the balance between fatty acids oxidation into mitochondria and lipids storage as triglycerides. This balance is mainly regulated by malonyl CoA (generated by acetyl-CoA carboxylase), which inhibits carnitine palmitoyltransferase-1 (CPT-1) and subsequent transport of fatty acids into mitochondria (Fig. 3). Activated AMPK inhibits malonyl CoA synthesis and shifts the balance towards mitochondrial fatty acid oxidation and away from fat storage. Depletion of lipid tissue content is associated with an improvement of in vivo metabolic parameters in insulin resistant rodent
models or in humans [10,11]. This suggests that depletion of ectopic adipose tissue (as observed after AMPK activation) is a promising therapeutic strategy for the management of metabolic syndrome and type 2 diabetes.

4. Regulation of myocardial ischaemia

The metabolic syndrome is associated with an increased risk of cardiovascular event and coronary heart disease mortality [2]. The role of AMPK on cardiac energy metabolism is particularly relevant in the setting of cardiac ischaemia and hypoxia [12]. Dramatic metabolic consequences are observed after total cessation of myocardial blood flow. In a few seconds, oxidative phosphorylation and mitochondrial ATP production are seriously disturbed inducing a decrease of high-energy phosphates, creatine phosphate and ATP levels. Enhanced lipolysis following catecholamine secretion increases free fatty acids uptake by ischaemic myocardium. Failure of mitochondrial oxidation by hypoxia is associated with cytosolic accumulation of free fatty acid CoA-esters, subsequent inhibition of glycolysis and decrease of anaerobic energy production [13]. Since AMPK regulates the balance between glucose and fatty acid metabolism at the cellular level, activation of AMPK could be a new therapeutic strategy to limit cellular damage during heart ischaemia. Indeed, hearts from AMPKα2-/- mice (or from transgenic mouse model overexpressing a dominant negative form of AMPKα2 in the heart) displayed a more rapid onset of ischaemic contracture than wild type mice, which was associated with a decrease in ATP content, in lactate production, in glycogen content and in the phosphorylation state of acetyl CoA carboxylase (ACC) [14]. These studies indicate that the α2 isoform of AMPK is required for the metabolic response of the heart to ischaemia suggesting that AMPK is cardioprotective. In addition, new data obtained in mouse models strongly suggest an important role of adiponectin as a cardioprotective adipokine through AMPK-dependent mechanisms [15,16]. Deletion of adiponectin in mice induces increased heart damage after reperfusion that was associated with diminished AMPK signalling in the myocardium [16,17]. In humans, the protective cardiovascular effects of adiponectin are more controversial. Blood levels of adiponectin in humans have been associated [18] or not [19] with a lower risk of heart attack. Nevertheless, these findings suggest that AMPK activation could be an important mechanism for the reduction of cell damage during heart ischaemia in vivo. Indeed, AMPK stimulates glycolysis and sustains energy supply during the ischaemic stress. Promotion of glucose oxidation in ischaemic/reperfused hearts could be a promising novel therapeutic approach of myocardial ischaemic condition. Such mechanism has been demonstrated during the phenomenon called ischaemic preconditioning [12], a situation known to induce endogenous protective mechanisms in heart muscle. Reconditioning ischaemia activates AMPK in a PKC-dependent manner and promotes glucose utilization in myocardial cells supporting resistance toward ischaemic consequences. Thus, cardiac-specific AMPK activators could be of particular interest for the management of myocardial ischaemia.

5. Regulation of lipid metabolism in the liver

AMPK has been also involved in the regulation of lipid metabolism. In the cholesterol synthesis pathway, AMPK blocks the conversion of HMG-CoA to mevalonate [3]. ACC is an important rate-controlling enzyme for the synthesis of malonyl-CoA, which is both a critical precursor for biosynthesis of fatty acids and a potent inhibitor of mitochondrial fatty acid oxidation. Inhibition of ACC by AMPK leads to a fall in malonyl-CoA content and a subsequent decrease in fatty acids synthesis. Liver-specific AMPKα2 deletion leads to increased plasma triglyceride levels and enhanced hepatic lipogenesis [20]. Conversely, overexpression of AMPKα2 in the liver decreases plasma triglyceride levels [21]. Decreased triglyceride levels have also been observed during AICAR infusion in lean and obese rodents [22]. This emphasizes the critical role
of AMPKα2 subunit for the control of hepatic lipogenesis, which is a pathway not adequately, controlled by AMPKα1 subunit. This suggests that AMPKα2 subunit is critical for the inhibition of hepatic lipogenesis and substitution by AMPKα1 subunit is not possible.

Studies in humans and various animal models have suggested that efforts to enhance insulin sensitivity might improve fatty liver disease, a situation frequently observed in patients with metabolic syndrome. The efficacy of metformin as a treatment for fatty liver disease has been confirmed in obese, ob/ob mice, which develop hyperinsulinemia, insulin resistance and fatty livers [10]. In contrast the effect of metformin as a treatment for fatty liver disease has not been confirmed in humans [23]. In addition, adiponectin restores insulin sensitivity and decreases hepatic steatosis by lowering triglyceride content in muscle and liver in obese mice [24]. Metabolic improvement of adiponectin is linked to an activation of AMPK in the liver decreasing fatty acids biosynthesis and increasing mitochondrial fatty acid oxidation [25]. This has been confirmed by decrease of liver triglyceride content in lean and obese rodents during AICAR infusion [26] and treatment with thienopyridone, a class of small molecule AMPK activators [26]. However, the role of the AMPK system in the treatment of fatty liver diseases remains to be clearly established in humans. Its importance is strongly indicated by recent successes in treating these disorders with therapies that activate AMPK including use of leptin or TZDs [23,27,28].

6. Regulation of hepatic glucose production

Increased hepatic glucose production is a key factor in type 2 diabetes. Since AMPK is usually considered as part of a mechanism involved in energy sparing, a potential role for AMPK in the regulation of the energy-consuming process of hepatic gluconeogenesis (de novo synthesis of glucose from three-carbon precursors) has been considered. Results obtained with pharmacological compounds and adenovirus-mediated AMPK activation / inactivation strategies have demonstrated that AMPK plays a role in the control of glucose production by the liver. Thus, liver-specific AMPKα2/-/- mice, which exhibited hyperglycaemia and glucose intolerance, presented increased fasting hepatic glucose production [20], demonstrating that hepatic AMPKα2 isoform is essential to suppress hepatic glucose production and maintain fasting blood glucose levels in the physiological range. AMPK activation by systemic infusion of AICAR [22] or by metformin [29] or by adenovirus expressing a constitutively active form of AMPKα2 (AMPKα2-CA) reduced glucose output [21]. It has been recently demonstrated that the ability of metformin to suppress hepatic glucose production and to lower blood glucose levels requires LKB1/AMPK signals [30]. The potent effects of circulating adipocyte-derived hormones on whole-body glucose metabolism recently highlighted the involvement of AMPK in the control of glucose output by the liver. Indeed, a physiological link has been established between increased resistin plasma levels (as observed in insulin resistant rodent models) and increased liver glucose output through AMPK activity inhibition [31]. Furthermore, it was recently demonstrated that hypoglycaemic effect of adiponectin appears to be mediated by hepatic AMPK activation [25]. This was corroborated with the incapacity of adiponectin to regulate hepatic glucose production in the absence of the AMPKα2 subunit in the liver [20].

7. Regulation of β-cell insulin secretion

The pathogenesis of type 2 diabetes is complex. A progressive decrease of β-cell function leads to glucose intolerance, which is followed by type 2 diabetes that inexorably aggravates with time. Physiological regulation of insulin secretion by AMPK is still discussed. AMPKα2 KO mice presented altered glucose regulation associated with a reduction in glucose-mediated insulin secretion [32]. This defect, only observed in vivo and not in isolated pancreatic islets of AMPKα2 KO mice, is dependent on excess in sympathetic tone (linked to AMPKα2 deletion in the hypothalamus) and was completely reversed when mice were treated with an α blocker drug. Because glucose-mediated insulin secretion was preserved in vitro, this model showed that the lack of pancreatic AMPKα2 subunit is not essential for the regulation of insulin secretion or might be compensated by remaining pancreatic catalytic AMPKα1 subunit. In contrast, pharmacological activation of AMPK has been shown to inhibit insulin secretion in vitro but only when chronically administered [33]. These results have been confirmed using adenovirus-mediated over-expression of constitutively active AMPK (AMPK-CA) in β-cell [34]. This inhibitory effect of AMPK on insulin secretion is associated with an increase in apoptotic index in β-cell. Potential regulation of β-cell mass by AMPK needs further studies.

8. Regulation of appetite/food intake

Hypothalamic AMPK regulates food intake: fasting is associated with an increase in AMPK activity in various hypothalamic nuclei whereas refeeding inhibits it [35]. Activation of hypothalamic AMPK by fasting, injection of recombinant adenoviruses expressing constitutively active (CA) AMPK in basal medial hypothalamus, cannabinoids and ghrelin is sufficient to increase food intake and body weight [35]. This effect is due to increase in neuropeptide Y (NPY) and agouti-related peptide (AgRP) expression in arcuate nucleus and in melanin-concentrating hormone expression in lateral hypothalamus [35]. Inhibition of hypothalamic AMPK by refeeding, dominant negative (DN) AMPK adenovirus injection and leptin reduces both food intake and body weight by decreasing NPY and AgRP expression pathway in arcuate nucleus [35]. Thus, changes in hypothalamic neuropeptides expression may simply explain how AMPK regulates food intake. Other anorexigenic hormones (such as insulin and leptin) or compounds (such as α-lipoic acid, an antioxidant drug that reduces food intake) inhibit AMPK activity but in other hypothalamic
regions than previously described above. In addition, hypotha-
lamic AMPK is also regulated coordinately with changes in peripheral AMPK activity; fed condition inhibits AMPK activ-
ity both in hypothalamus and in peripheral tissues due to an excess of calories. AMPK actions on both orexigenic and anor-
exigenic pathways in hypothalamus are mediated by the classi-
celular AMPK network: acetyl-CoA carboxylase, malonyl-
-CoA cellular content and subsequent modulation in mitochon-
drial fatty acids oxidation [35]. Thus, reduction of food intake
following AMPK inhibition is linked to increase in malonyl-
-CoA concentration and subsequent decrease in hypothalamic fatty acids oxidation. In the same way, a direct inhibition of hypothalamic CPT-1 infusing pharmacological inhibitors is sufficient to decrease food intake indicating the crucial role of lipid oxidation in regulation of food intake by hypothalamic AMPK.

9. Action of anti-diabetic drugs on the AMPK pathway

The growing evidence that AMPK could switch metabolism from an anabolic state, favoring the synthesis and storage of glucose and fatty acids, to a catabolic state, favoring the oxidation of these fuel molecules, led to propose in 1999 that AMPK activators might be effective treatments for type 2 diabetes. This was soon tested by in vivo treatment with AICAR of various animal models of insulin resistance, such as genetically obese mice (ob/ob) and rats (fa/fa), or rats fed a high-fat diet. Encouragingly, the drug was found to reverse most, if not all, of the metabolic abnormalities of these animals. Thus, it caused improvements in glucose tolerance, decreases in plasma fatty acids and triglycerides, decreases in hepatic glucose output and blood pressure, increases in glucose disposal and HDL cholesterol, and even a tendency toward reduction of abdominal fat [3]. Furthermore, we have recently demonstrated that short-term activation of AMPK signalling pathway specifically in the liver is sufficient to decrease food intake indicating the crucial role of lipid oxidation in regulation of food intake by hypothalamic AMPK. 

10. AMPK as a new pharmacological target: conclusion and medical perspectives

AMPK system plays a major role in the regulation of glucose and lipid metabolism through its acute effects on energy metabolism pathways. By maintaining energy balance, both at the single cell and the whole body levels, AMPK appears as an important player in the alterations of energy metabolism that occur in conditions like the metabolic syndrome. It is already well established that AMPK activation by pharmacological compounds (metformin, TZDs), adipokines (leptin, adiponectin) or physical activity causes many metabolic changes that would be beneficial for subjects with the metabolic syndrome, such as increased glucose uptake and metabolism by muscle and other tissues, decreased glucose production by the liver, and decreased synthesis and increased oxidation of fatty acids. Thus, the net effect of AMPK activation would be beneficial for the treatment of Type 2 diabetes and insulin resistance. This concept was further supported by studies done in animal models of insulin resistance, showing that chronic AMPK activation improves metabolic parameters of these animals. Furthermore, recent data from human studies have suggested that the metabolic effects of metformin in subjects with type 2 diabetes may be mediated by the activation of AMPK [40]. Nevertheless, the widespread and various cellular function of AMPK make its selective targeting in therapeutics a difficult one with simultaneous, both advantageous and deleterious consequences possible. Indeed, an emerging concept is that the result of AMPK activation is context specific and can be either beneficial or deleterious, depending on the tissue, degree of stimulation or conditions of activation. Potential negative effects of chronic AMPK activation include glycogen accumulation in the heart, inhibition of insulin secretion and increases in appetite and body weight. A therapeutic agent would ideally activate AMPK in peripheral tissues (to increase fatty acid oxidation and glucose uptake and reduce gluconeogenesis) while inhibiting it in the hypothalamus (to reduce food intake and body weight). Alternatively, the development of tissue-selective activators of AMPK is of direct interest. As a matter of fact, analysis of the in vivo tissue distribution of the nopyridone, a recently identified class of small AMPK activators [26], revealed that this compound reached the highest concentration in liver with much lower levels in other tissue. Based on the tissue distribution of this compound, it is likely that improvements of overall glucose and lipid metabolism observed in diabetic mice chronically treated with this compound are primarily due to stimulation of AMPK in liver. This finding is remarkably reminiscent of the results obtained with liver specific overexpression of a constitutively active
form of AMPKα2 in obese and diabetic mouse models [21]. Thus, these data strengthen the hypothesis that AMPK activation primarily directed to liver can affect whole-body intermediary metabolism and highlights many of the expected benefits of tissue-specific AMPK activation. Obviously, additional studies utilizing direct and selective AMPK activators are required to map all the regulatory elements of the AMPK signalling pathway, identify its regulatory actions, and elucidate how this pathway functionally integrates with other intracellular pathways and cellular actions to further supports the potential of AMPK as a drug target for the treatment of diabetes and the metabolic syndrome in humans.

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