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Review Article

Adenosine monophosphate–activated protein kinase in diabetic nephropathy

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A B S T R A C T

Diabetic nephropathy (DN) is the leading cause of end-stage renal disease, and its pathogenesis is complex and has not yet been fully elucidated. Abnormal glucose and lipid metabolism is key to understanding the pathogenesis of DN, which can develop in both type 1 and type 2 diabetes. A hallmark of this disease is the accumulation of glucose and lipids in renal cells, resulting in oxidative and endoplasmic reticulum stress, intracellular hypoxia, and inflammation, eventually leading to glomerulosclerosis and interstitial fibrosis. There is a growing body of evidence demonstrating that dysregulation of 5′ adenosine monophosphate–activated protein kinase (AMPK), an enzyme that plays a principal role in cell growth and cellular energy homeostasis, in relevant tissues is a key component of the development of metabolic syndrome and type 2 diabetes mellitus; thus, targeting this enzyme may ameliorate some pathologic features of this disease. AMPK regulates the coordination of anabolic processes, with its activation proven to improve glucose and lipid homeostasis in insulin-resistant animal models, as well as demonstrating mitochondrial biogenesis and antitumor activity. In this review, we discuss new findings regarding the role of AMPK in the pathogenesis of DN and offer suggestions for feasible clinical use and future studies of the role of AMPK activators in this disorder.

Introduction

Diabetes, especially type 2 diabetes, is now a global epidemic that reflects the harmful consequences of modern lifestyles. Consumption of processed, high-calorie foods, along with physical inactivity, has created an imbalance between energy intake and expenditure [1,2]. This disruption of energy balance is characterized by shifts in lipid and glucose metabolism manifesting as fasting and postprandial hyperglycemia together with dyslipidemia and is further promoted by insulin resistance in a number of tissues [3]. Chronic exposure to glucose overload, free fatty acids, and amino acids can be toxic [4]. Chronic kidney disease (CKD) associated with diabetes is a relatively common manifestation, with both the prevalence and incidence rising in recent years [5]. CKD is the end result of multifactorial processes that mostly stem from deranged glucose and lipid metabolism. This is demonstrated by the increased expression of proteins in relevant signaling pathways and consistent pathologic renal findings. Many studies and experiments have been devised to elucidate the pathogenesis of these metabolic disruptions, although emerging concepts related to such findings remain vast and vague. In an attempt to unravel the core of this disease entity, a growing body of evidence shows that dysregulation of 5′ adenosine

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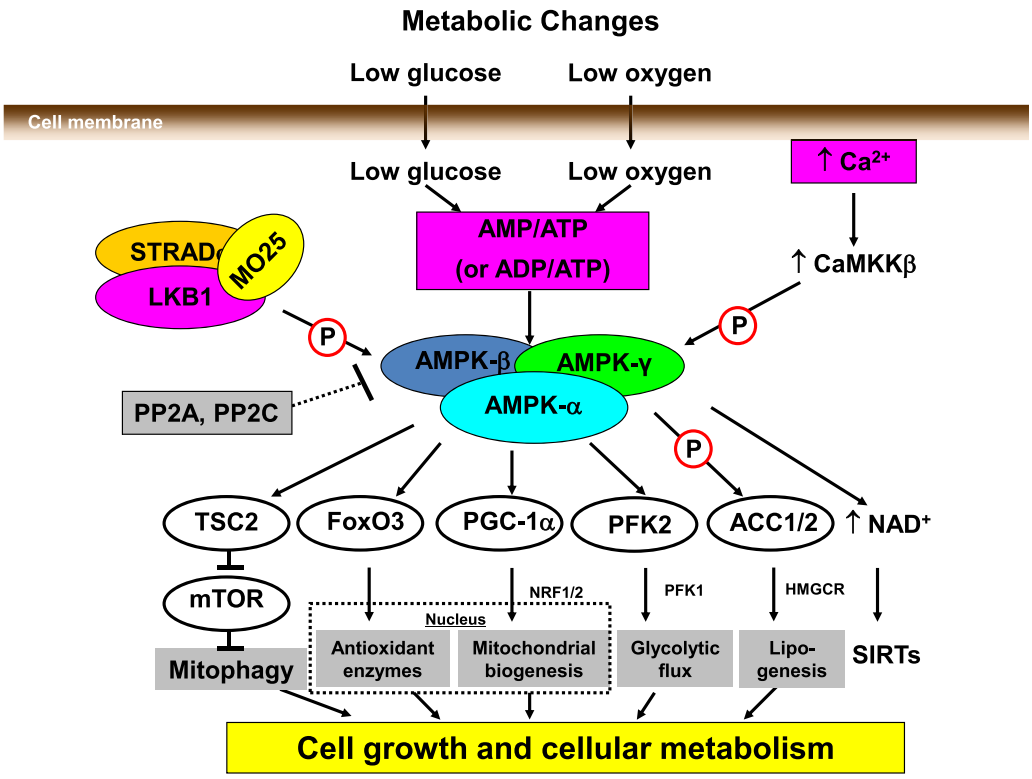

Figure 1. Regulation of AMPK by metabolic stress, LKB1, and intracellular Ca^{++}. The AMPK signaling pathway responds to energy stresses that cause fluctuations and imbalances in the AMP/ATP (or ADP/ATP) ratio. As the ATP level falls, there is an increase in the AMP level, which triggers the activation of the AMPK pathway. The upstream regulator of AMPK, LKB1, allows for AMP phosphorylation at a specific site (Thr-172) on the α subunit of AMPK. Two other subunits, STRAD and MO25, form a complex with LKB1 to enhance this process. CaMKK, which is induced by an increase in intracellular Ca^{++}, is also able to activate AMPK. Of the CaMKK proteins, CaMKKβ has the strongest regulatory effect on AMPK. CaMKKβ regulates AMPK in response to changes in surrounding energy stresses.

ACC, acetyl-CoA carboxylase; ADP, adenosine diphosphate; AMP, adenosine monophosphate; AMPK, 5′ adenosine monophosphate–activated protein kinase; ATP, adenosine triphosphate; CaMKKβ, Ca^{++}/calmodulin-dependent protein kinase kinase β; FoxO3, forkhead box O3; HMGCR, 3-hydroxy-3-metylglutaryl-CoA reductase; LKB1, liver kinase B-1; MO25, mouse protein 25; mTOR, mammalian target of rapamycin; NAD, nicotinamide adenine dinucleotide; NRF, nuclear respiratory factor; PGC-1α, peroxisome proliferator–activated receptor-gamma coactivator 1α; PFK2, phosphofructokinase 2; PP2A, protein phosphatase 2A; PP2C, protein phosphatase 2C; SIRTs, sirtuins; STRAD, *STE*-related adaptor; Thr-172, threonine-172; TSC2, tuberous sclerosis complex 2.

monophosphate–activated protein kinase (AMPK) in relevant tissues is crucial to the development of metabolic syndrome and diabetes [6]. Therefore, targeting this enzyme is a matter of great interest, as it may ameliorate some of the pathologic features of the disease. AMPK regulates the coordination of anabolic processes with its activation proven to improve glucose and lipid homeostasis in insulin-resistant animal models [7,8]. AMPK is strongly expressed in the kidney, where it is involved in diverse physiological and pathologic processes, including ion transport, podocyte function, and diabetic renal hypertrophy. In light of this, we have looked for novel agents that would help to modulate AMPK in an organ-specific manner that targets the diabetic kidney. Instead of providing an exhaustive review of the role of AMPK in these pathologies, this review aims to discuss the mechanisms of AMPK agonists in the context of diabetic nephropathy (DN) and, therefore, shed light on the risks and benefits of currently available and promising future AMPK activators as a treatment option.

AMPK: structure and mechanism of action

AMPK is a metabolic master switch that regulates downstream signals based on shifts in the surrounding energy reservoir [6]. It is expressed in a number of tissues, including the kidney, the liver, the skeletal muscle, the adipose tissue, and the hypothalamus of the brain [9,10]. It is activated when adenosine triphosphate (ATP) consumption causes an increase in the adenosine monophosphate (AMP)-to-ATP ratio [6]. For example, under such conditions as hypoglycemia, exercise, hypoxia, and ischemia, in which accentuated cellular signaling cascade and intracellular stress arise, consumption of ATP is suppressed while production is spurred [11]. Regulation of AMPK activation can be achieved through either allosteric activation by AMP or stimulation by upstream kinases, including a compound consisting of 3 proteins: *STE*-related adaptor (STRAD), mouse protein 25, and the tumor-suppressor liver kinase B1 (LKB1) [12]. In addition, other enzymes, such as Ca^{++}/calmodulin-dependent protein kinase kinase β (CaMKKβ) [13] and transforming growth factor (TGF) β-activated kinase [14], also participate in the cellular signaling cascade (Fig. 1). On activation, AMPK signals through its downstream substrates to achieve energy homeostasis by stimulating processes that generate ATP through such actions as fatty acid oxidation and glucose transport, while inhibiting those that use ATP through the opposing actions of fatty acid synthesis and protein synthesis [12]. Thus, the net effect of AMPK activation is an increased cellular energy level via the